Traitement des infections liées à *P. aeruginosa*

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canton de vaud
LIBERTÉ ET PATRIE

A comparison of microbiology and demographics among patients with healthcare-associated, hospital-acquired, and ventilator-associated pneumonia: a retrospective analysis of 1184 patients from a large, international study

Andrew A Quartin[1,2,3], Ernesto G Scerpella[4], Sailaja Puttagunta[4] and Daniel H Kett[1,2,3*]

- ✓ *Pseudomonas aeruginosa* was the most common Gram-negative organism isolated in all pneumonia classes
  - HCAP, 22/199 (11.1%)
  - HAP, 28/379 (7.4%)
  - VAP, 57/606 (9.4%);

Table 2 Microbiology grouped by HCAP, HAP, and VAP[a]

Microbiology	HCAP (n = 199) n (%)	HAP (n = 379) n (%)	VAP (n = 606) n (%)
Gram-positive pathogens	117 (58.8)	226 (59.6)	441 (72.8)
MRSA	82 (41.2)	125 (33.0)	259 (42.7)
MSSA	12 (6.0)	51 (13.5)	107 (17.7)
Pneumococcus	4 (2.0)	10 (2.6)	15 (2.5)
Other *Streptococcus* spp.	7 (3.5)	15 (4.0)	18 (3.0)
Gram-negative pathogens	53 (26.6)	113 (29.8)	222 (36.6)
Pseudomonas aeruginosa	22 (11.1)	28 (7.4)	57 (9.4)
Acinetobacter spp.	8 (4.0)	16 (4.2)	44 (7.3)
Haemophilus spp.	6 (3.0)	5 (1.3)	23 (3.8)
Moraxella catarrhalis	4 (2.0)	1 (0.3)	2 (0.3)
Klebsiella spp.	5 (2.5)	32 (8.4)	41 (6.8)
Escherichia coli	10 (5.0)	19 (5.0)	17 (2.8)
Enterobacter spp.	3 (1.5)	15 (4.0)	31 (5.1)
Proteus mirabilis	1 (0.5)	8 (2.1)	13 (2.1)
Stenotrophomonas maltophilia	0 (0)	2 (0.5)	13 (2.1)
Polymicrobial	111 (55.8)	191 (50.4)	387 (63.9)
Culture negative	50 (25.1)	101 (26.6)	79 (13.0)
Bacteremia	28 (14.1)	49 (12.9)	103 (17.0)

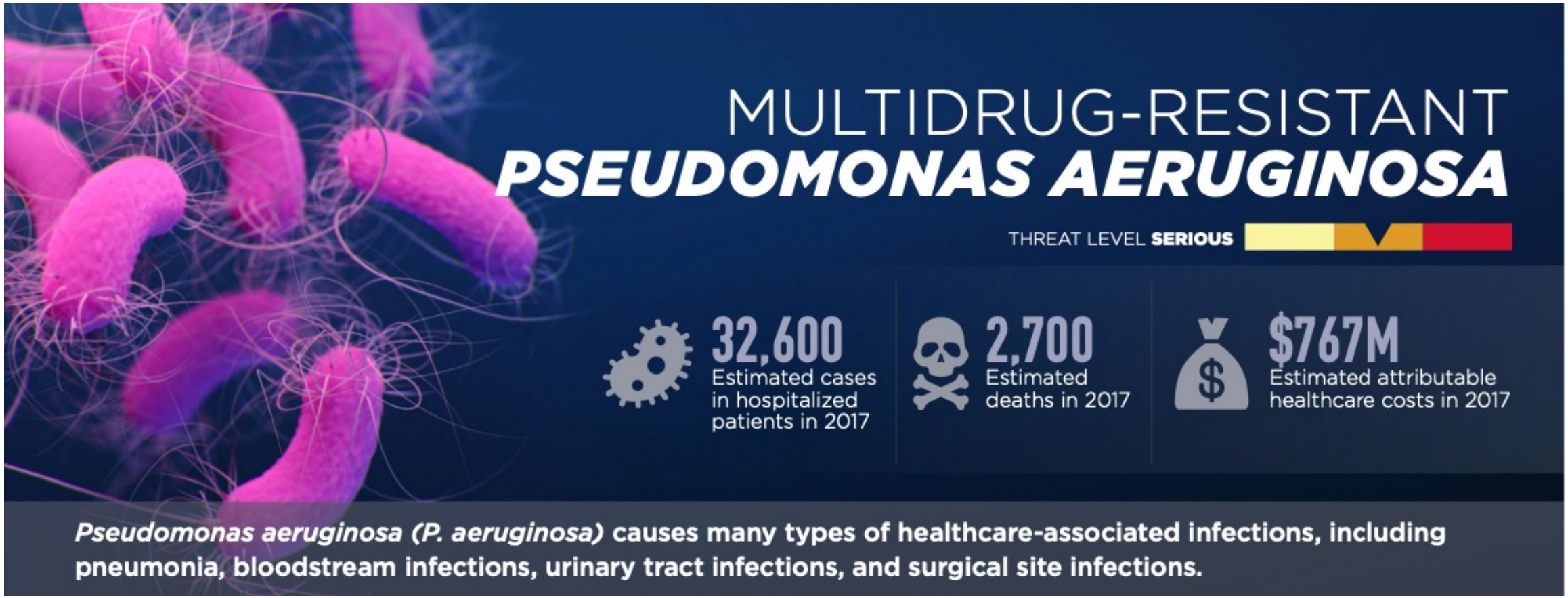
Quartin et al, BMC Infectious Diseases 2013, 13:

Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study

Table 1. Most common etiological pathogens isolated from patients with VAP, as documented in a prospective observational study that enrolled patients from 27 ICUs in nine European countries

Causative pathogen	VAP[a] (*n* = 465)	
	Early VAP (<5 days; *n* = 193)	Late sVAP (≥5 days; *n* = 272)
Unknown, *n* (%)	48 (24.9)	61 (22.4)
Other, *n* (%)	43 (22.3)	26 (9.6)
Staphylococcus aureus, *n* (%)	58 (30.1)	58 (21.3)
MRSA, *n* (%)	18 (9.3)	34 (12.5)
MSSA, *n* (%)	40 (20.7)	24 (8.8)
P. aeruginosa, *n* (%)	26 (13.5)	55 (20.2)
Acinetobacter spp., *n* (%)	16 (8.3)	56 (20.6)
Enterobacteriaceae, *n* (%)	61 (31.6)	92 (33.8)
Polymicrobial infection, *n* (%)	50 (25.9)	64 (23.5)

Koulenti et al, Eur J Clin Microbiol Infect Dis 2017;


MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA
THREAT LEVEL SERIOUS
32,600
Estimated cases in hospitalized patients in 2017
2,700
Estimated deaths in 2017
$767M
Estimated attributable healthcare costs in 2017
Pseudomonas aeruginosa (P. aeruginosa) causes many types of healthcare-associated infections, including pneumonia, bloodstream infections, urinary tract infections, and surgical site infections.

Plan

- ✓ Sensibilité & PK/PD
- ✓ EUCAST…..
- ✓ Nouvelles molécules
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

Antibiotiques avec une activité contre *Pseudomonas*

ß-lactamines

- ticarcilline ± clavu
- pipéracilline ± tazo
- aztréonam
- cefsulodine
- céfopérazone
- ceftazidime
- cefpirome
- céfépime
- **ceftolozane-tazobactam**
- **ceftazidime-avibactam**
- imipénème
- ✍ méropénème
- ✍ **cefiderocol**
- ✍**Meropenème- vaborbactam**
- ✍**Imipenem-cilastatine-relebactam**

Aminosides

- gentamicine
- nétilmicine
- tobramycine
- amikacine

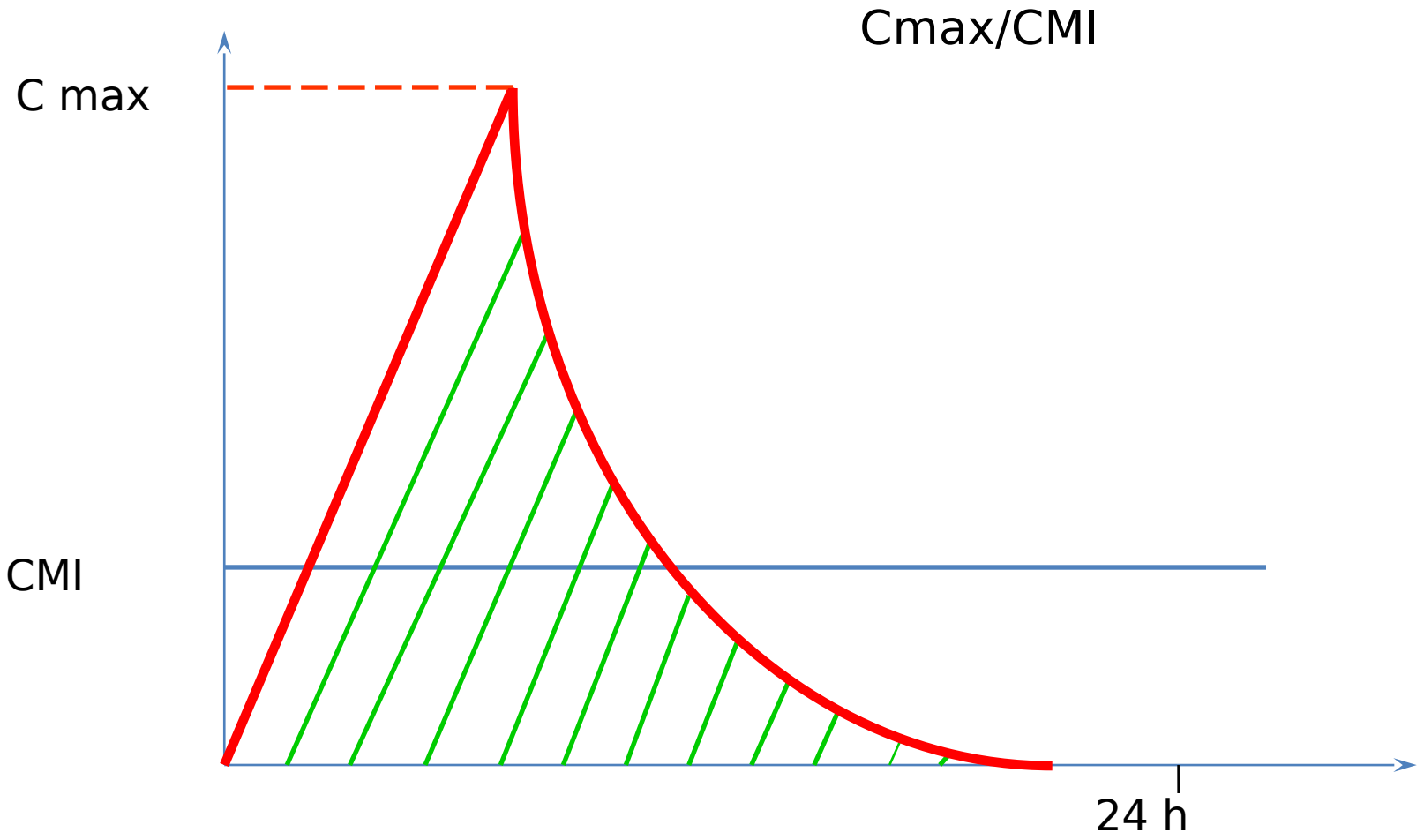
Fluoroquinolones

- ciprofloxacine
- ✍ lévofloxacine
- ✍ delafloxacine

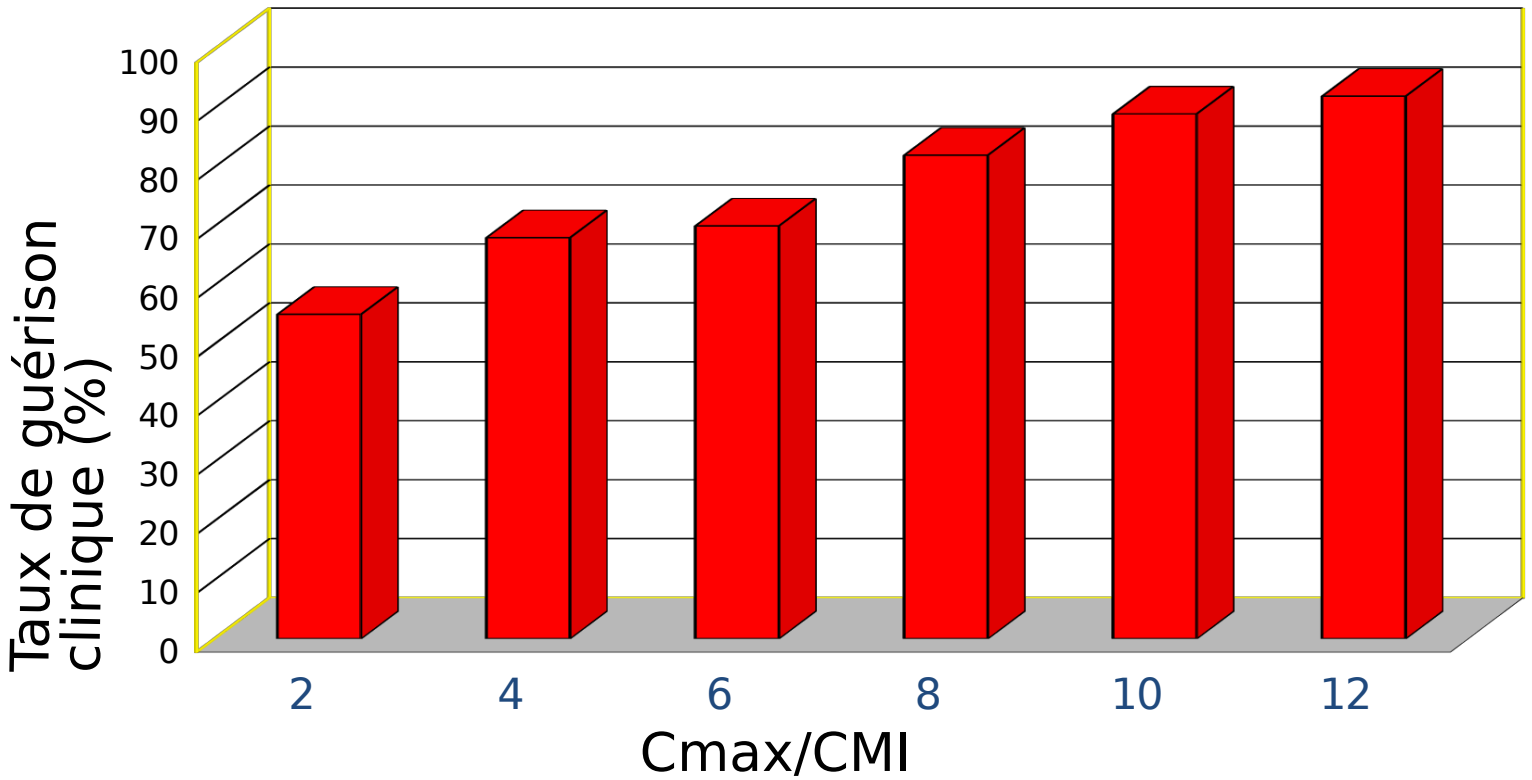
Autres

- colistine
- polymyxine B
- rifampicine
- fosfomycine

Aminosides

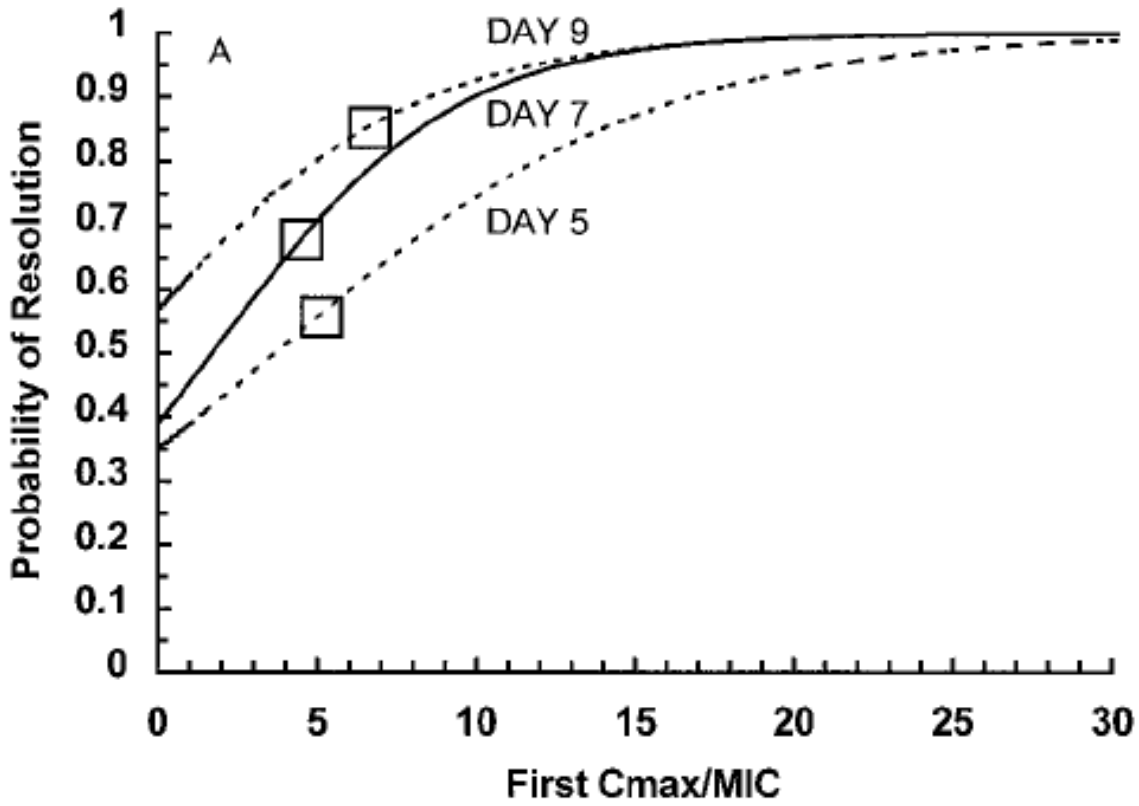


Aminosides
Relation Cmax/CMI - Guérison clinique



Moore, JID 1987

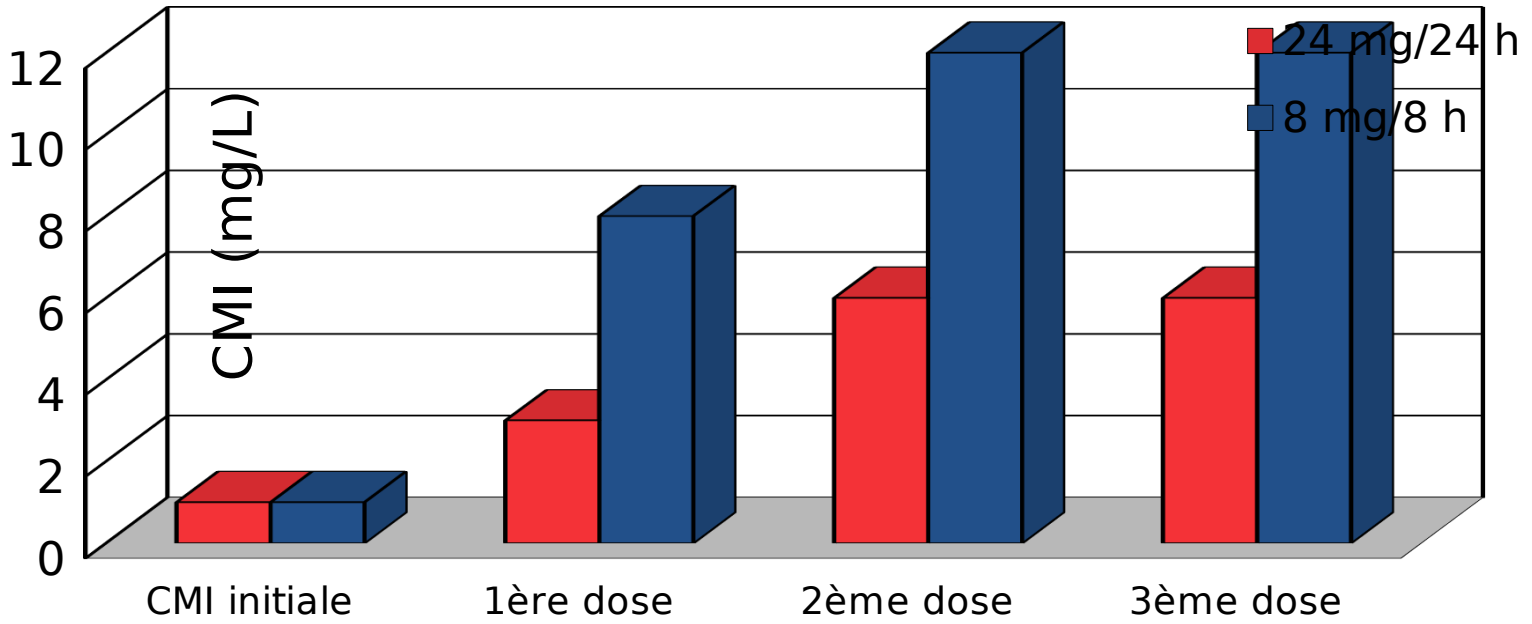
Importance de la première dose d'aminoside sur l'évolution clinique



Kashuba et al, AAC, 199

Résistance adaptative

CMI; modèle statique *in vitro*

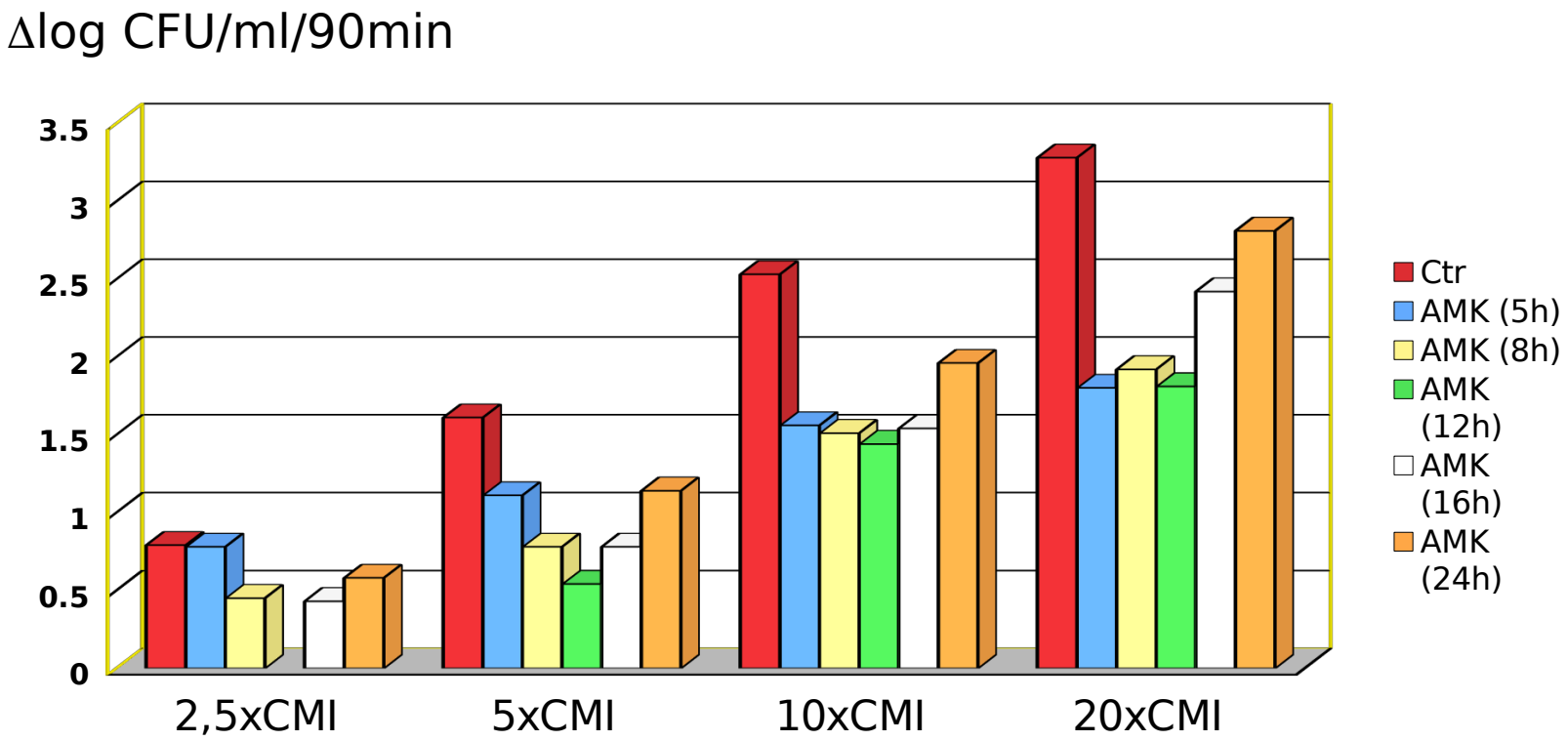


tobramycine

P. aeruginosa

Karlowsky et al, JAC 1994

Résistance adaptative



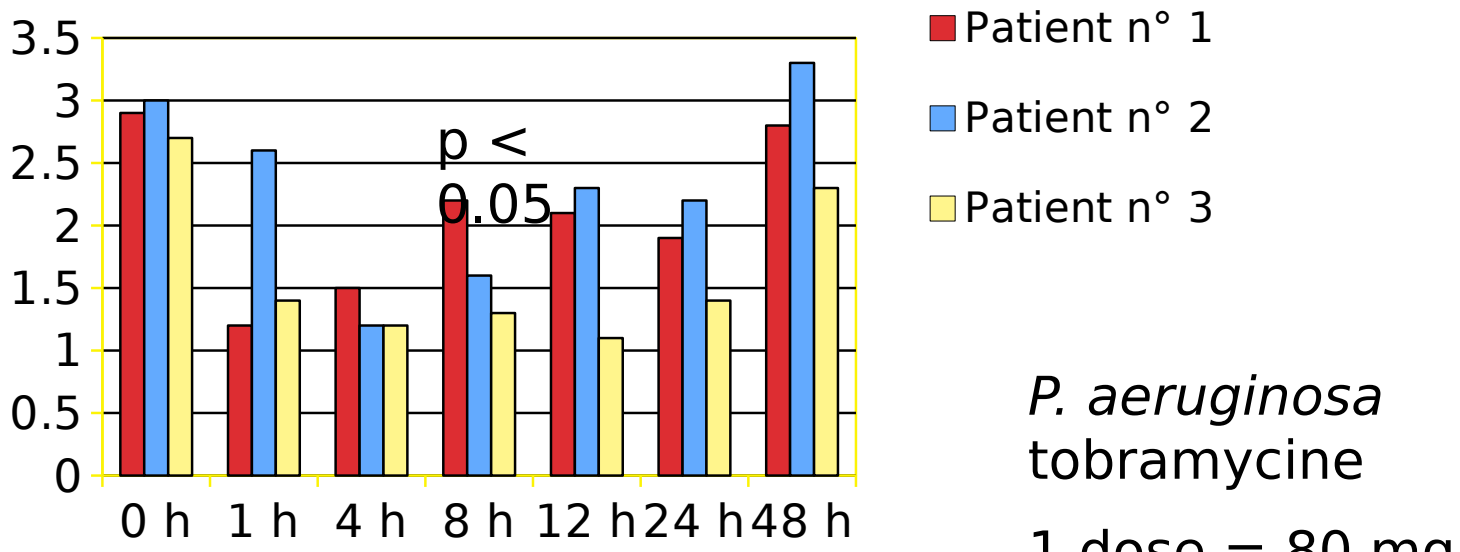
AMK in vivo : 80 mg/kg

Xiong et al, AAC 199

Résistance adaptative

Mucoviscidose

Bactéricidie (log10 CFU/ml)



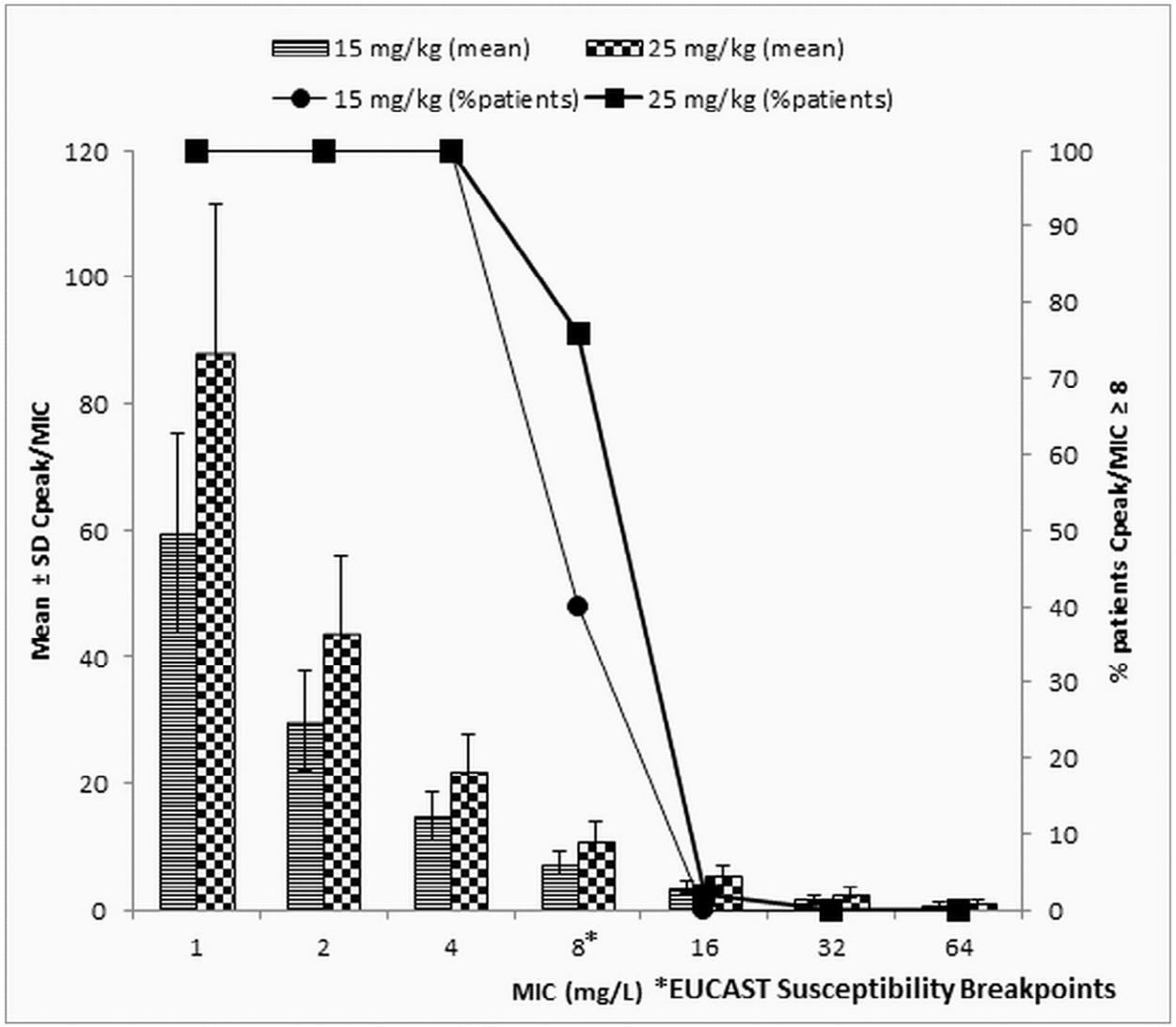
P. aeruginosa
tobramycine

1 dose = 80 mg

Barclay et al, JAC 1996

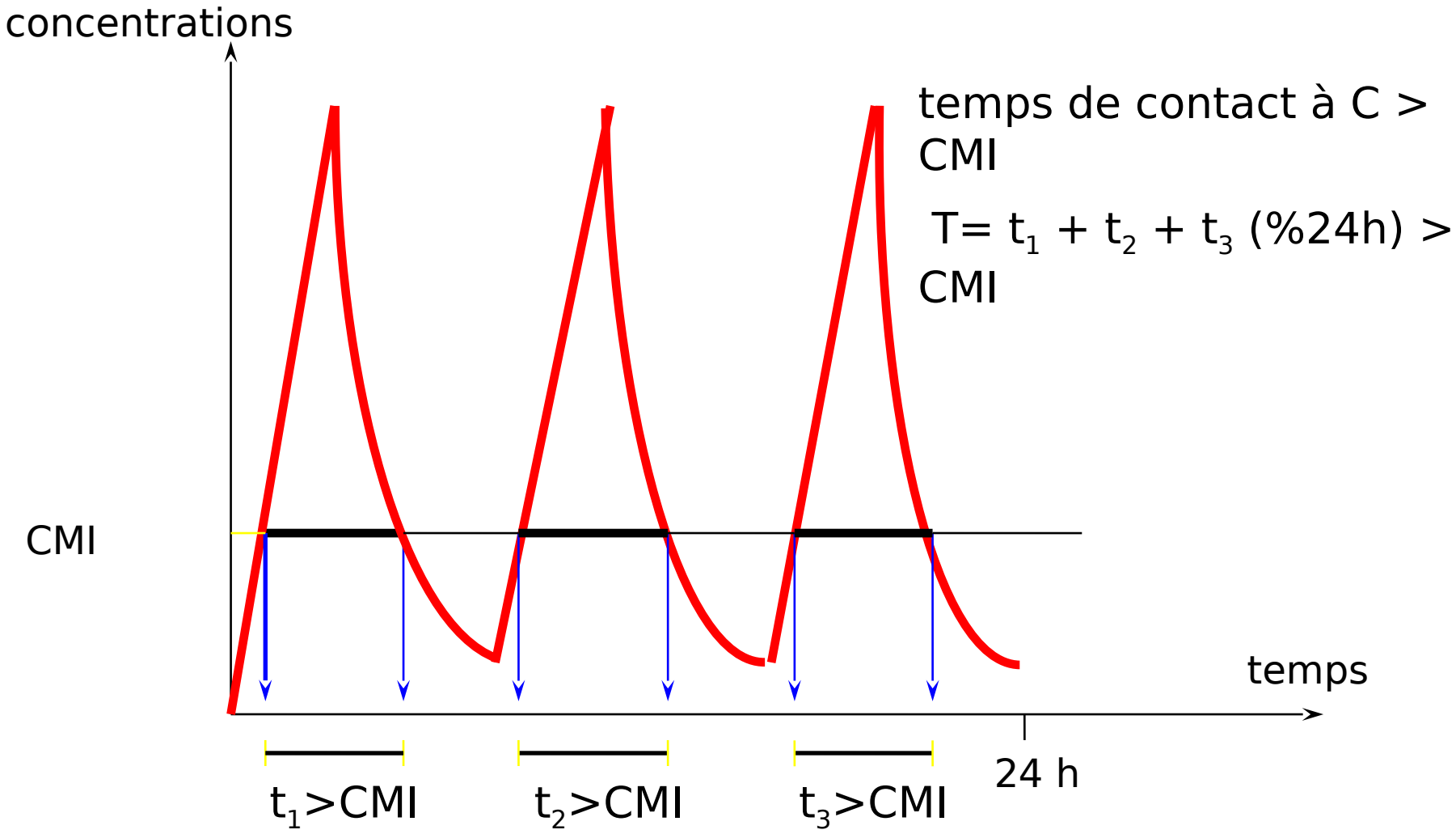
Higher versus standard amikacin single dose in emergency department patients with severe sepsis and septic shock: a randomised controlled trial

- ✓ Prospective randomised controlled study
- ✓ Severe sepsis or septic shock treated with 15 mg/kg versus 25 mg/kg amikacin.
- ✓ The primary outcome target attainment defined as Cpeak/MIC ≥ 8
- ✓ 104 patients included. The target was attained in 76% vs. 40% of patients assigned to the 25 mg/kg vs. 15 mg/kg dose groups (P < 0.0001).

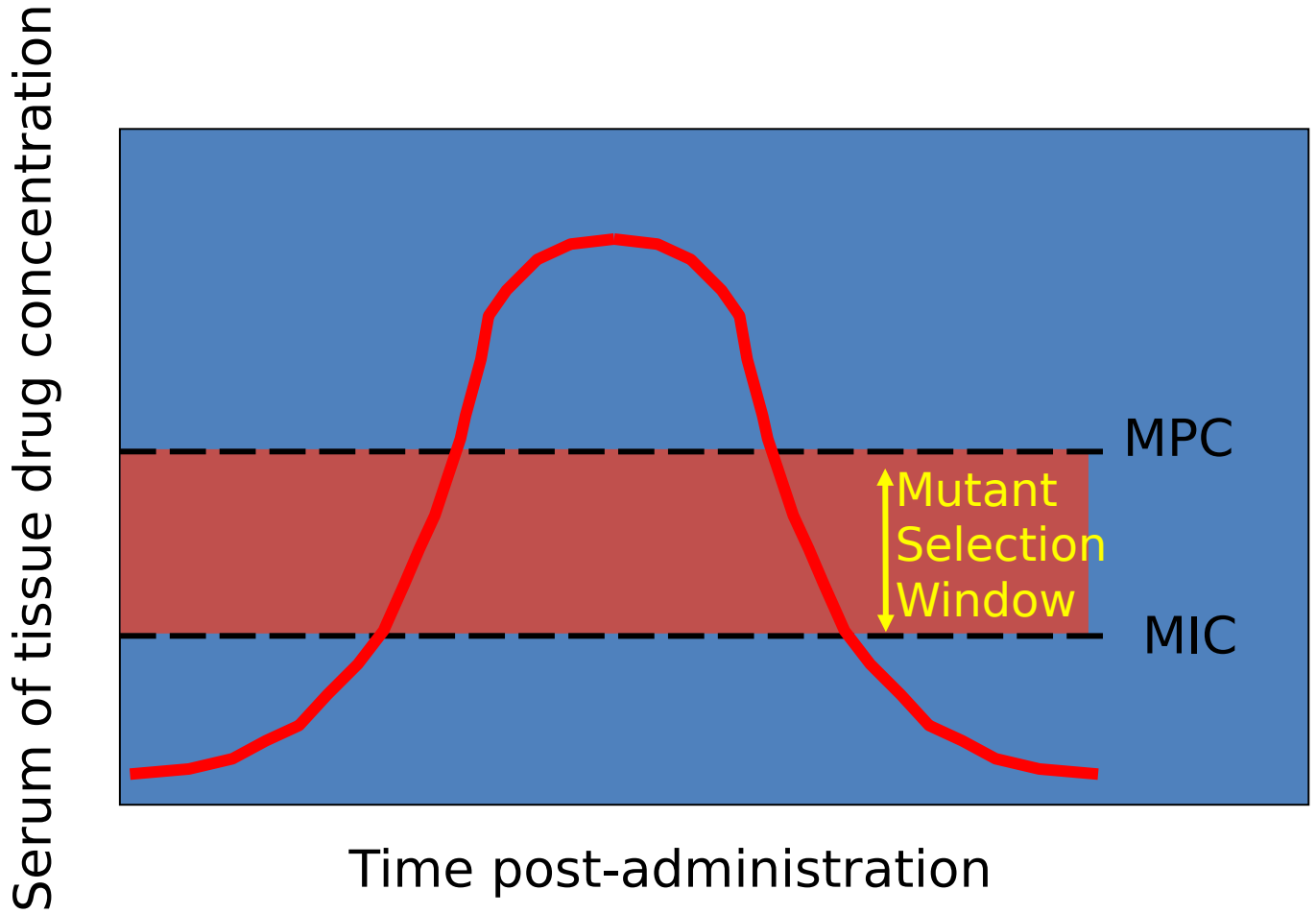


De Winter et al, International Journal of Antimicrobial Agents 51 (2018)

Bêtalactamines:
paramètres pharmacodynamiques



Craig et al, CID 200



- ✓ Idealized sketch of serum or tissue drug concentration after administration of a single dose of antibiotic to a patient.
  - MIC and mutant prevention concentration (MPC), determined in laboratory studies, are indicated.
  - The area between MPC and MIC (shaded) represents the mutant selection window

- ✓ 18 patients de réanimation
- ✓ Dose de charge 12mg/kg, suivie de 6 g/24 h de ceftazidime
  - soit en continu (n=8)
  - soit en 3 bolus de 2g/8h (n = 10)
- ✓ Durant les 8 premières heures, concentrations sériques < 40 mg/L (5 fois la conc. crit. inf):
  - groupe perfusion continue: 1 patient / 8 (38 mg/L)
  - groupe bolus: 8 patients / 10 (2 - 33 mg/L)
- ✓ Durant les 40 heures suivantes, temps avec des concentrations sériques > 40 mg/L:
  - groupe perfusion continue: 100%
  - groupe bolus: 20 - 30%

Lipman, JAC 1999; 43: 309-11

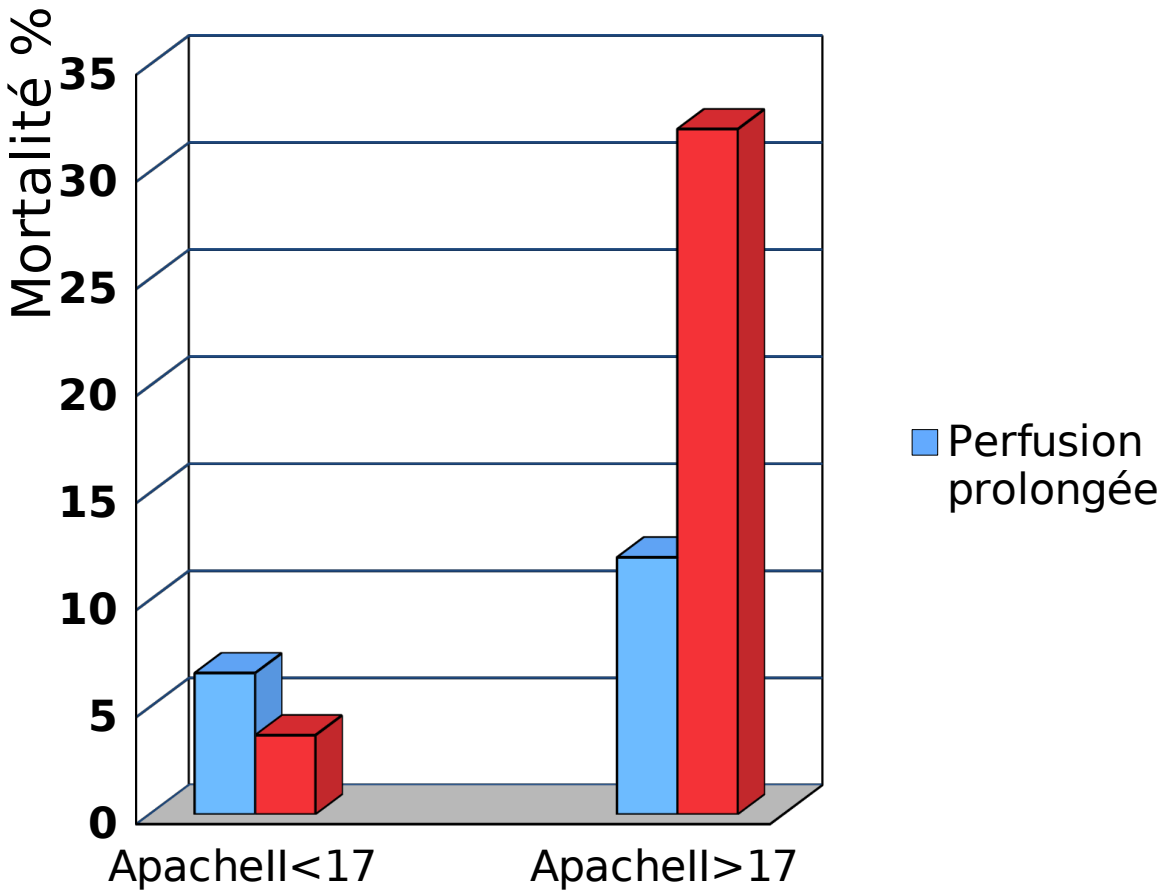
Extended-Infusion Cefepime Reduces Mortality in Patients with *Pseudomonas aeruginosa* Infections

- ✓ Single-center study compared cefepime for bacteremia and/or pneumonia
  - ✓ admitted from 1 January 2008 through 30 June 2010 (a 30-min infusion of 2 g every 8 h)
  - ✓ admitted from 1 July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h).
- ✓ Extended infusion was associated to
  - ✓ **Decreased mortality (20% versus 3%; p=0.03).**
  - ✓ Decreased mean length of stay of 3.5 days less
  - ✓ Decreased mean length of stay was significantly less in the extended-infusion group (18.5 days versus 8 days; P0.04).
  - ✓ Decreased Hospital costs were $23,183 less per patient,
- ✓ Extended-infusion treatment with cefepime provides increased clinical and economic benefits in the treatment of invasive P*. aeruginosa* infections.

Bauer et al, Antimicrob Agent Chemother 2013, 57, 2

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

- ✓ Étude sur cohorte de 194 patients
- ✓ Deux modalités d'administration
  - 3.375g en 30 min toutes les 4 à 6 H
  - 3.375g en 4 H toutes les 8 H
- ✓ Analyse de 2 paramètres en fonction du Score Apache II
  - Mortalité
  - Durée d'hospitalisation



Lodise et al , CID, 200

Meropenem Dosing Based on a Population Pharmacokinetic–Pharmacodynamic Model in Elderly Patients with Infection of the Lower Respiratory Tract

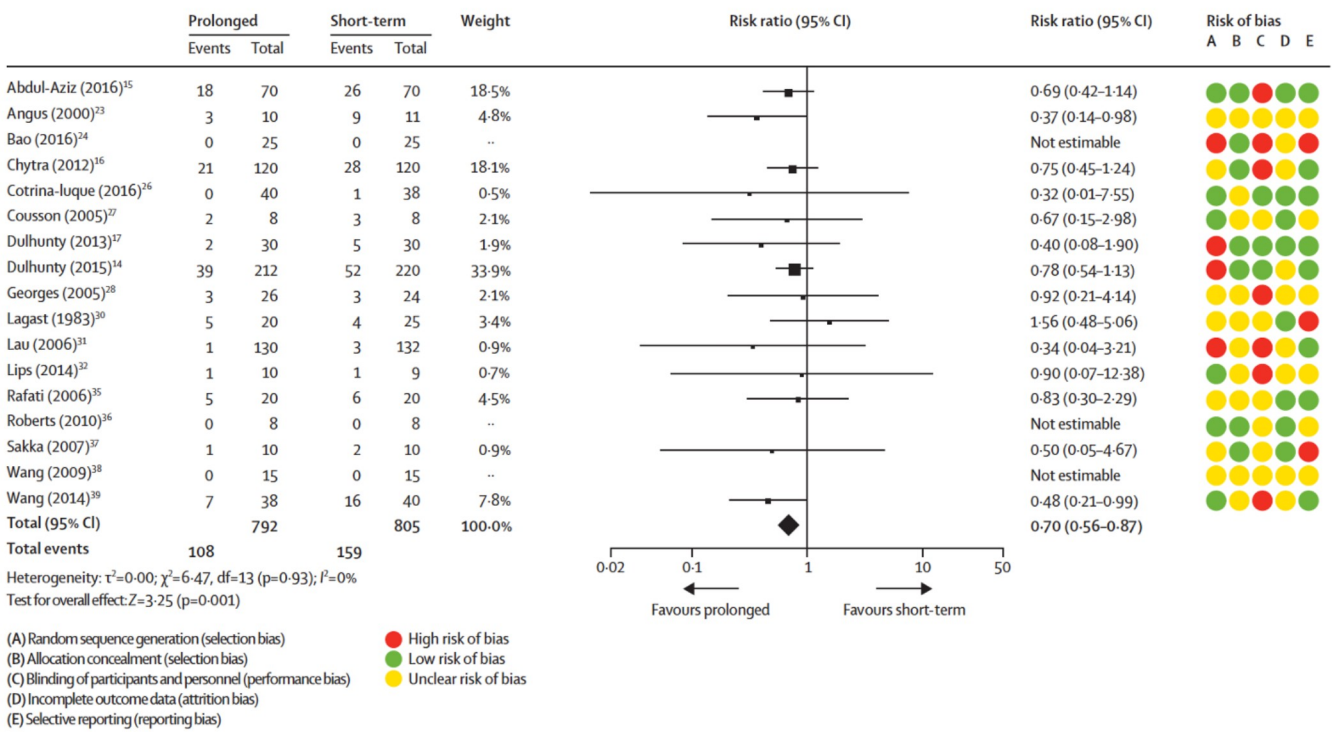
- ✓ Prospective single-center open-label randomized controlled trial
- ✓ 79 elderly patients with an LRTI caused by Gram-negative bacilli
- ✓ Treatment
  - Meropenem according to a regimen decided by the attending physician.
  - Individualized meropenem therapy with a dosing strategy based on software developed from a meropenem population PK/PD model (prolonged 3h infusion)

Characteristics	All patients ($n = 79$)	Study group ($n = 39$)	Control group ($n = 40$)	Odds ratio (95% CI)	p value
Daily meropenem dose (g)	1.5 (1.5–3.0)	1.5 (1.5–2.0)	2.0 (1.5–3.0)	–	0.017
Duration of meropenem therapy (days)	9.0 (7.0–13.0)	10.0 (7.0–13.0)	9.0 (7.0–13.0)	–	0.665
Total meropenem dose (g)	18.0 (10.5–26.0)	15.0 (7.5–24.0)	19.0 (12.0–29.5)	–	0.090
$T_{>MIC}$	98.9 (76.3–100.0)	98.9 (77.1–100.0)	79.7 (52.3–100.0)	–	0.105
Clinical success	63 (79.7)	35 (89.7)	28 (70.0)	0.780 (0.620–0.981)	0.029
Bacteriologic success	52 (65.8)	28 (71.8)	24 (60.0)	0.836 (0.607–1.151)	0.269

Zhou et al, Drugs Aging 2017;34:1

Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials

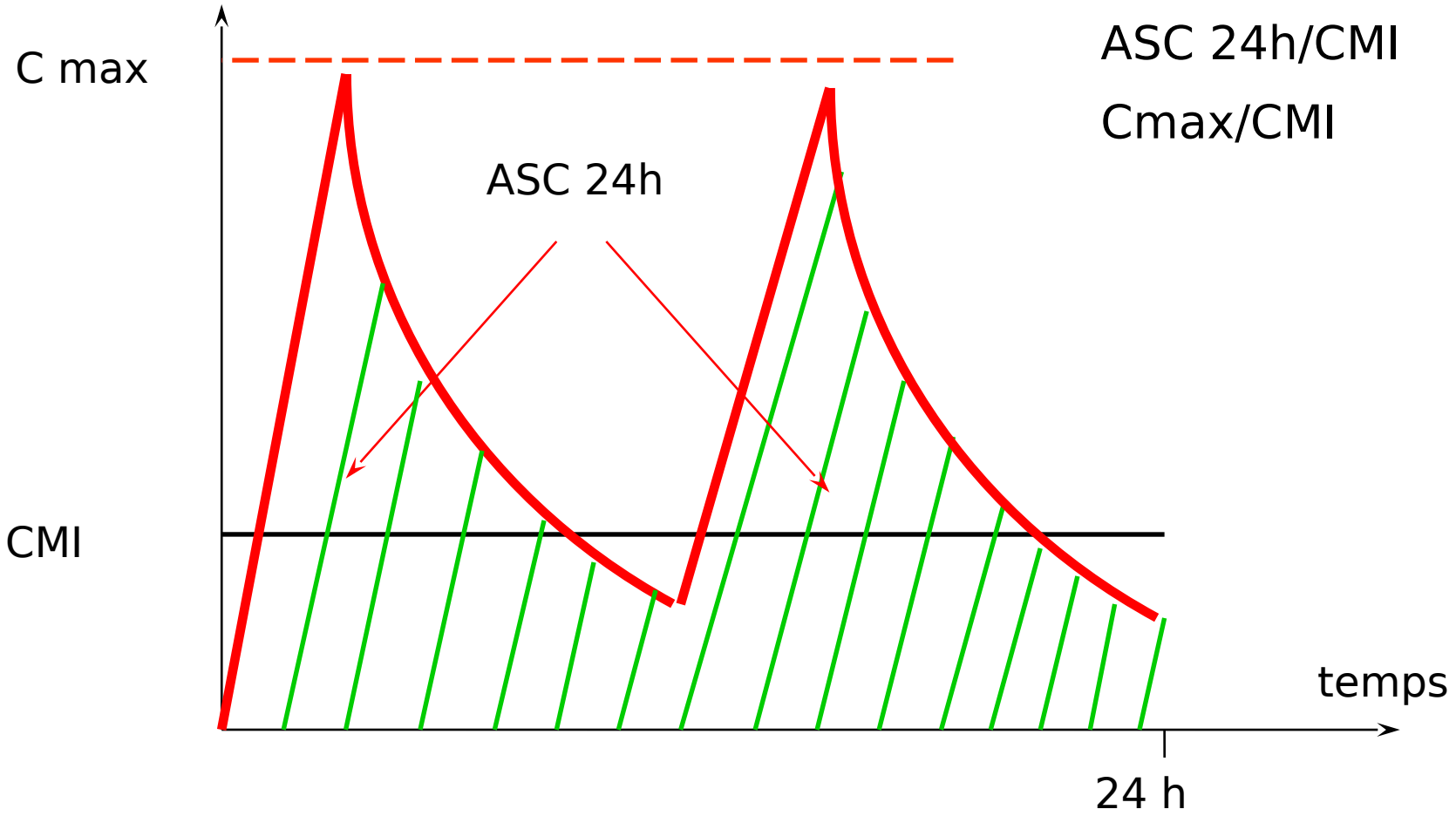
- Systematic review and meta-analysis
- RCT comparing mortality or clinical efficacy of antipseudomonal β-lactams for the treatment of patients with sepsis
  - Prolonged (continuous or ≥3 h)
  - Short-term (≤60 min) infusion
- 2196 articles were identified and screened, and 22 studies (1876 patients) included in the meta-analysis



Prolonged infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion

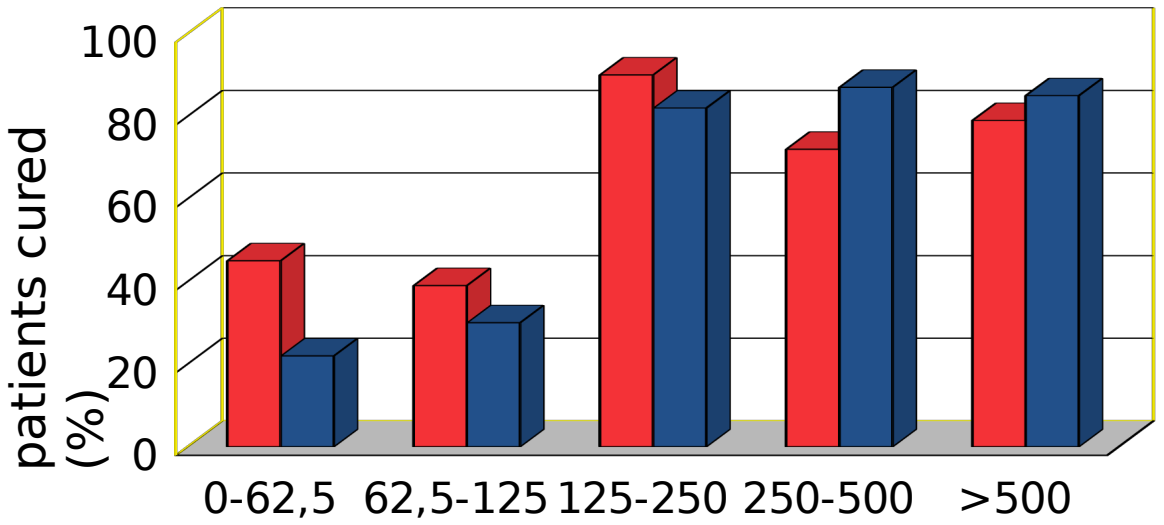
Vardakas et al, Lancet Inf Dis 2018;18:108

Fluoroquinolones



Fluoroquinolones

Relation ASC 24h/CMI et efficacité



64 patients

ciprofloxacine

Clinical

Bacteriologic

Forrest, AAC 1993

Table 1. Relationship of the ratio of 24-h area under the curve to MIC (24-h AUC/MIC ratio) and monotherapy and combination therapy to the emergence of resistant organisms during therapy with β-lactams and ciprofloxacin.

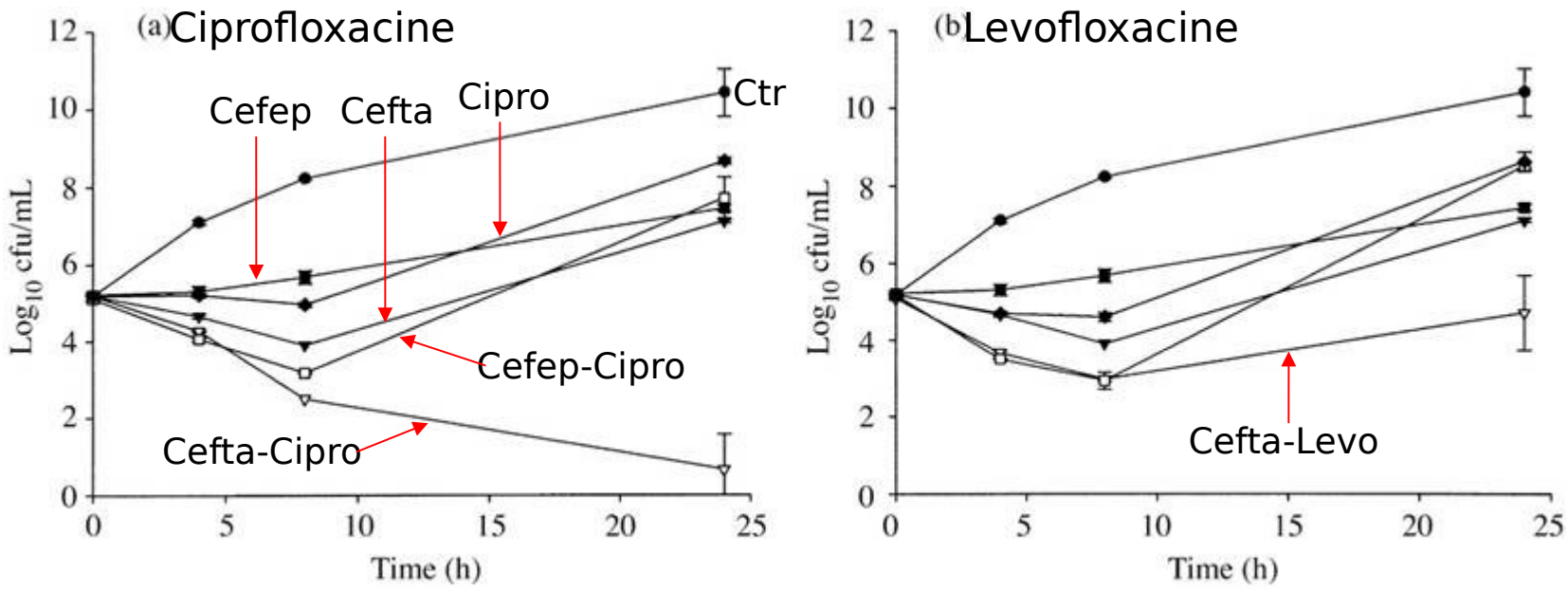
Therapy	24-h AUC/MIC ratio	Patients with resistance/ total patients (%)		
		All patients	Ciprofloxacin treatment	β-Lactam treatment
Monotherapy	<100	14/17 (82)	12/14 (86)	2/3(67)
Monotherapy	⩾100	17/84 (20)	4/44 (9)	13/40 (31)
Combination	⩾100	1/27 (4)	0/16 (0)	1/27 (4)

Craig et al CID 200

Table 2. Relationship of the 24-h area under the curve to MIC (24-h AUC/MIC ratio) to the emergence of resistant *Pseudomonas* and other gram-negative bacilli (GNB) during monotherapy with ciprofloxacin and β-lactams.

24-h AUC/MIC ratio	Patients with resistance/total patients (%)			
	Ciprofloxacin therapy		β-Lactam therapy	
	Pseudomonas	Other GNB	*Pseudomonas*	Other GNB
<100	10/10 (100)	2/4 (50)	2/3 (67)	
⩾100	2/8 (25)	2/28 (7)	2/3 (67)	10/28 (36)
P	.002	.07	2/3 (67)	

Craig et al CID 200



Synergic activity of cephalosporins plus fluoroquinolones against *Pseudomonas aeruginosa* with resistance to one or both drugs.

Fish et al, JAC 2002

Delafloxacin: a novel fluoroquinolone with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*

Table 2. Susceptibility test interpretive criteria for delafloxacin [4].

	Minimum inhibitory concentrations (μg/mL)			Disk diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Staphylococcus aureus	≤0.25	0.5	≥1	≥23	20–22	≤19
Staphylococcus haemolyticus	≤0.25	0.5	≥1	≥24	21–23	≤20
Streptococcus pyogenes	≤0.06	–	–	≥20	–	–
Streptococcus agalactiae	≤0.06	0.12	≥0.25	–	–	–
Streptococcus anginosus Group	≤0.06	–	–	≥25	–	–
Enterococcus faecalis	≤0.12	0.25	≥0.5	≥21	19–20	≤18
Enterobacteriaceae	≤0.25	0.5	≥1	≥22	19–21	≤18
Pseudomonas aeruginosa	≤0.5	1	≥2	≥23	20–22	≤19

S = susceptible; I = intermediate; R = resistant.

Table 5. Clinical outcomes of delafloxacin for acute bacterial skin and skin-structure infections in Phase III trials [4,19,20,22].

Trial	Delafloxacin	Vancomycin 15 mg/kg + Aztreonam	Treatment difference (2-sided 95% CI)
Trial 1	**300-mg**	**intravenous**	
Total *N*	331	329	
Clinical response, *n* (%)	259 (78.2%)	266 (80.9%)	−2.6 (−8.8 to 3.6)
Success ITT, *n* (%)	270 (81.6%)	274 (83.3%)	−1.7 (−7.6 to 4.1)
Success CE, *n/N* (%)	232/240 (96.7%)	238/244 (97.5%)	−0.9 (−4.3 to 2.4)
Trial 2	**300-mg**	**intravenous and 450-mg oral**	
Total *N*	423	427	
Clinical response, *n* (%)	354 (83.7%)	344 (80.6%)	3.1 (−2 to 8.3)
Success ITT, *n* (%)	369 (87.2%)	362 (84.8%)	2.5 (−2.2 to 7.2)
Success CE, *n/N* (%)	339/353 (96%)	319/329 (97%)	−0.9 (−3.9 to 2)
Trial 3	**300-mg**	**intravenous**	
Total *N*	331	329	
Objective response, *n* (%)	259 (787.2%)	266 (80.9)	−2.6 (−8.78 to 3.57)
Investigator assessed cure, *n* (%)	172 (52%)	166 (50.5%)	1.5 (−6.11 to 9.11)

CI = confidence interval; ITT = intent-to-treat and includes all randomized patients; CE = clinically evaluable consisted of all ITT patients who had a diagnosis of ABSSSI, received at least 80% of expected doses of study drug, did not have any protocol deviations that would affect the assessment of efficacy and had investigator assessment at the follow-up visit.

Ocheretyaner et al, Expert Review of Anti-infective Therapy 2018;1

Is fluoroquinolone monotherapy a useful alternative treatment for *Pseudomonas aeruginosa* bacteraemia?

- ✓ Retrospective study between Nov 2013 and Nov 2014 at Taipei Veterans General Hospital.
- ✓ 105 patients enrolled, 78 patients received beta-lactams and 27 received fluoroquinolones (20 with ciprofloxacin and 7 with levofloxacin)
- ✓ Primary bacteraemia (39.0%) and urinary tract infections (37.1%) were the most common sources of bacteraemia

Outcome	Total ($N=105$)	Fluoroquinolone group ($N=27$)	Beta-lactam group ($N=78$)	P value
28-day mortality	28 (26.7)	3 (11.1)	25 (32.1)	0.062
Bacteraemia-associated mortality	21 (20.0)	3 (11.1)	18 (23.1)	0.289
In-hospital mortality	35 (33.3)	5 (18.5)	30 (38.5)	0.097
Duration of definitive therapy, days[a]	11.5±4.9	11.6±4.6	11.5±5.1	0.731

- ✓ The 28-day mortality rate between the two groups stratified by APACHE II and Pitt bacteraemia scores showed no significant differences in each category
- ✓ Fluoroquinolone might be an alternative to beta-lactam as a definitive monotherapy for *P. aeruginosa* bacteraemia provided they are active in vitro

Wu et al, Infection 2018, 46:36

Plan

- ✓ Sensibilité & PK/PD
- ✓ EUCAST…..
- ✓ Nouvelles molécules
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

European Committee on Antimicrobial Susceptibility Testing
Breakpoint tables for interpretation of MICs and zone diameters
Version 10.0, valid from 2020-01-01

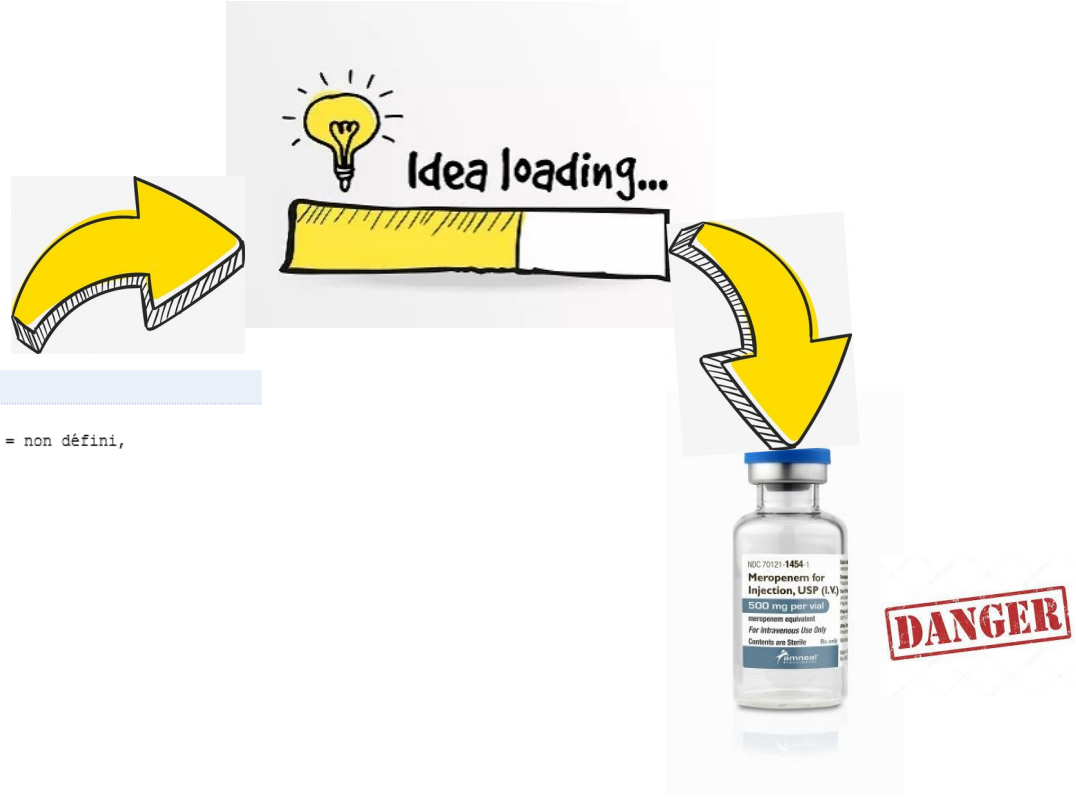
UNIL | Université de Lausanne
Faculty of Biology and Medicine

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

- ✓ MIC cut-offs for piperacillin-tazobactam, ceftazidime, cefepime changed to
  - S if MIC < 0.001 mg/L
  - R if > 16/8/8
- ✓ No change for meropenem (2/8)

- ✓ The aims of these changes were to highlight the need for increased dosages of antibiotics due to
  - the decreased wild-type pathogen susceptibility
  - acquired resistance
  - intrinsically less susceptible wild-pathogens

canton de vaud



Source de l'échantillon	HEMOCULTURE PONCTION VEINEUSE

Antibiogramme (micro)

S = Sensible, I = Sensible à une dose supérieure d'antibiotique, N = non défini,
R = Résistant

Antibiogramme	1
Pipéracillin-tazobactam	I
Ceftazidime	I
Cefepime	I
Imipenem	I
Meropenem	S
Amikacin	S
Tobramycin	S
Ciprofloxacin	I
Levofloxacin	I

1. Pseudomonas aeruginosa

Evaluate the impact of 2020 EUCAST modifications on the prescription of meropenem to treat Pseudomonas aeruginosa infections in Lausanne University Hospital

Munting et al, Clin Microbiol Infect 2022

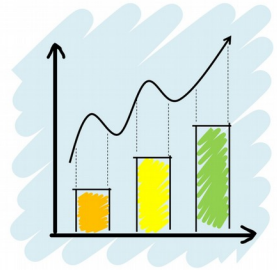
Methods

- ✓ Retrospective single-centre observational study in Lausanne University Hospital (CHUV)
- ✓ Between 01.08.2019 and 30.07.2020
- ✓ Inclusion:
  - ≥ 18 years old
  - Treatment for *P. aeruginosa* infections
  - Susceptibility testing available
  - Treatment possible with ceftazidime, cefepime or piperacilline-tazobactam
- ✓ Exclusion:
  - *P. aeruginosa* resistant to meropenem
  - Allergy to non-carbapenem beta-lactams

Munting et al, Clin Microbiol Infect 2022

Methods

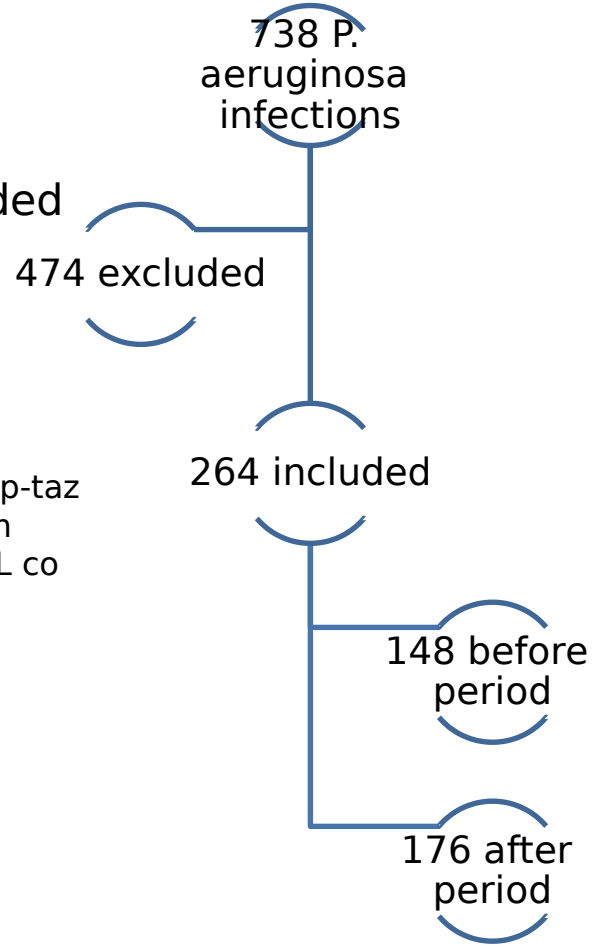
- ✓ Primary outcome
  - Prescription of meropenem to treat *P. aeruginosa* infections after release of susceptibility testing results
- ✓ Secondary outcomes
  - Use of increased dosage for non-meropenem anti-pseudomonal drugs
  - IDS consultations rates
- ✓ Statistical analysis
  - Univariable logistic regression to test for independent variables associated with the primary outcome.
  - Multivariable logistic regression using the LASSO method
  - Regression discontinuity analysis to test whether the increase in mropenem prescription rates was associated with the new EUCAST criteria



Munting et al, Clin Microbiol Infect 2022

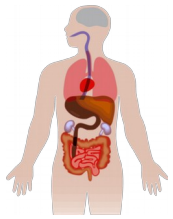
Results

- 70 <18 years old
- 54 susceptibility testing not recorded in EMR
- 291 no treatment targeted on *P. aeruginosa*
- 59 at least one exclusion criteria
  - 6 Penicillin allergy
  - 35 CI or resistance to cefta/cefep and pip-taz
  - 29 P aeruginosa resistant to meropenem
  - 13 GNB to all cefta/cefep/pip taz or ESBL co infection



Munting et al, Clin Microbiol Infect 2022

	Overall (n=264)	Before EUCAST update (n=148)	After EUCAST update (n=116)	*P*-value
Percentage male (%)	168 (63.6)	90 (60.8)	78 (67.2)	0.343
Age, mean (SD)	64.56 (18.72)	64.27 (18.81)	64.92 (18.69)	0.782
Patients' location (%)				0.1
Intensive care	32 (12.1)	14 (9.5)	18 (15.5)	
Outpatient	36 (13.6)	25 (16.9)	11 (9.5)	
Inpatients	196 (74.2)	109 (73.64)	87 (75)	
Site of infection (%)				0.696
Bacteraemia and endovascular infection	10 (3.8)	5 (3.4)	5 (4.3)	
Urinary tract	63 (23.9)	37 (25.0)	26 (22.4)	
Low respiratory tract	104 (39.4)	62 (41.9)	42 (36.2)	
Mucocutaneous	28 (10.6)	13 (8.8)	15 (12.9)	



Munting et al, Clin Microbiol Infect 2022

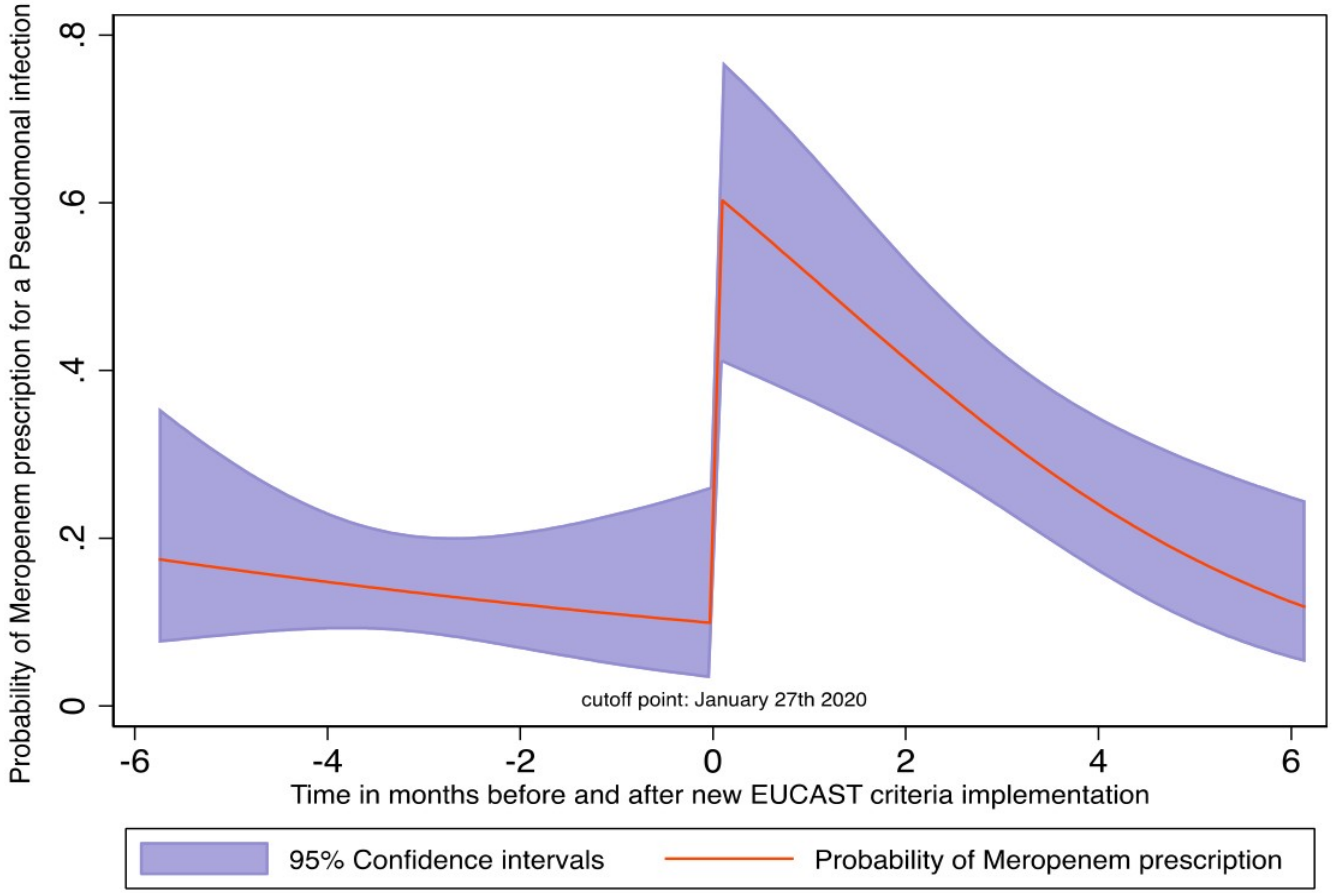
Table 3: Adjusted risk factors associated with meropenem prescription

	Overall (n=264)	No meropenem prescription (n=224)	Meropenem prescription (n=40)	Multivariate OR [95% CI]	*P* Value
Study period after new EUCAST criteria (%)	116 (43.9)	81 (36.2)	35 (87.5)	22.12 [7.96-79.52]	<0.001
Age > 65 years (%)	153 (58.0)	135 (60.3)	18 (45.0)	0.40 [0.17-0.94]	0.038
Cystic fibrosis (%)	13 (4.9)	9 (4.0)	4 (10.0)	5.78 [0.86-38.50]	0.067
Healthcare associated infection (%)	143 (54.2)	115 (51.3)	28 (70.0)	3.03 [1.27-7.83]	0.016
Gram-negative rod coinfection (%)	73 (27.7)	57 (25.4)	16 (40.0)	2.18 [0.92-5.18]	0.076
IDS consult after susceptibility testing (%)	87 (33.0)	79 (35.3)	8 (20.0)	0.20 [0.07-0.49]	0.001

EUCAST: European Committee on Antimicrobial Susceptibility Testing; IDS: Infectious Diseases Specialist.

Munting et al, Clin Microbiol Infect 2022

Discontinuity regression analysis

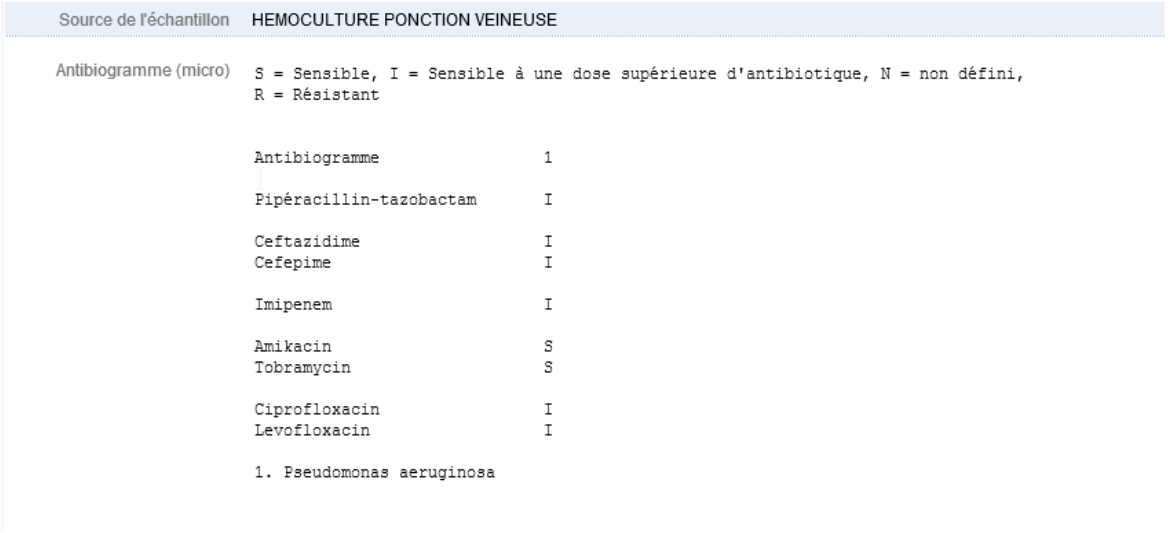


Munting et al, Clin Microbiol Infect 2022

Conclusions

- ✓ Higher proportion of meropenem prescriptions for the treatment of *P. aeruginosa* infections
- ✓ Infectious diseases consultations increased
- ✓ Limitations
  - Monocentric
  - 2 studies period not perfectly comparable

- ✓ Antimicrobial stewardship program
  - Changes in the rendering of susceptibility testing reports
  - Color code
  - Education
  - Authorisation



Source de l'échantillon	HEMOCULTURE PONCTION VEINEUSE
Antibiogramme (micro)	S = Sensible, I = Sensible à une dose supérieure d'antibiotique, N = non défini, R = Résistant

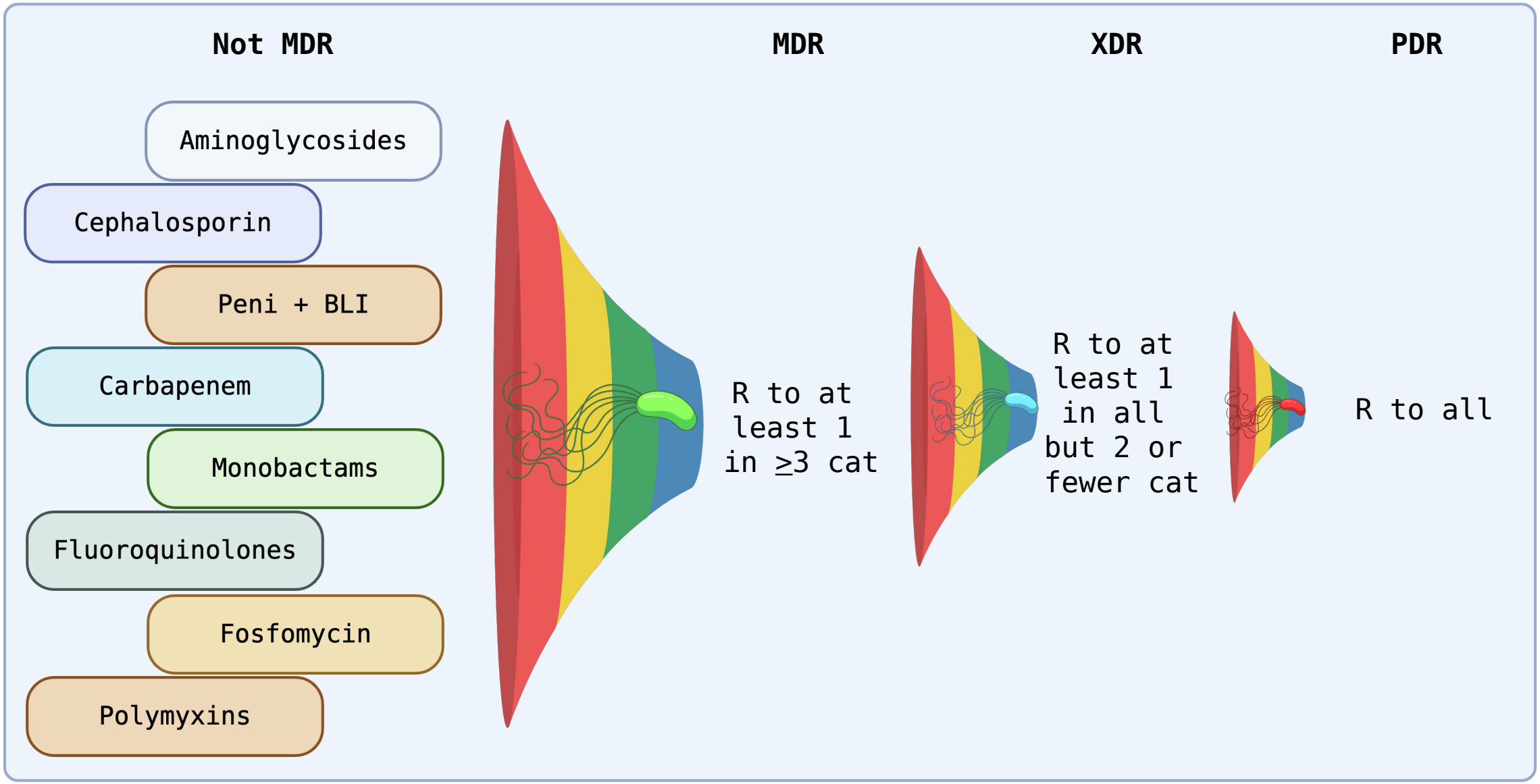
Antibiogramme	1
Pipéracillin-tazobactam	I
Ceftazidime	I
Cefepime	I
Imipenem	I
Amikacin	S
Tobramycin	S
Ciprofloxacin	I
Levofloxacin	I

1. Pseudomonas aeruginosa

Munting et al, Clin Microbiol Infect 2022

Plan

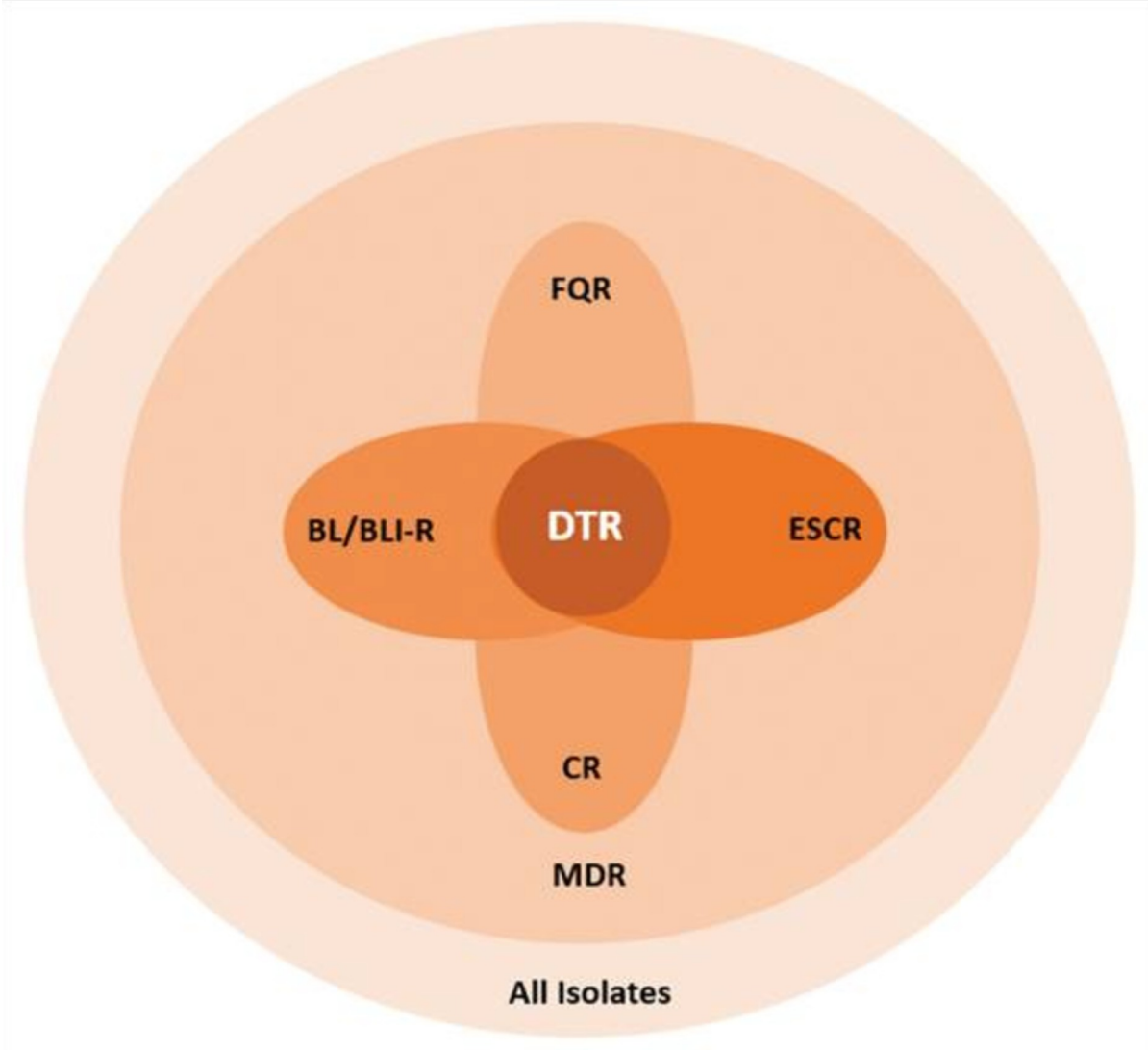
- ✓ Sensibilité & PK/PD
- ✓ EUCAST…..
- ✓ Nouvelles molécules
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives



Magiorakos et al, Clin Microbiol Infect 2012; 18: 268–281

DTR : résistance difficile à traiter

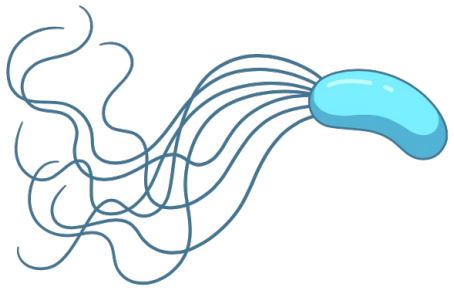
- Non-susceptibilité à tous les agents de première ligne
- Conduit à l'utilisation d'agents de seconde ligne (tels que les aminoglycosides, la tigécycline ou le polymyxines) caractérisés par des propriétés pharmacocinétiques moins favorables et un risque accru de toxicité
- Meilleure prédiction d'un mauvais pronostic

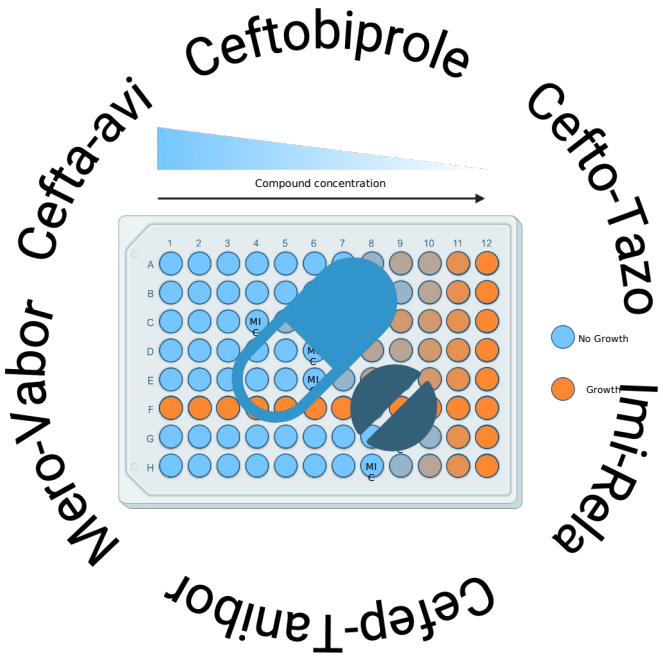


Fluoroquinolone resistance (FQR),
Extended-spectrum cephalosporin resistance (ESCR),
Carbapenem resistance (CR)

Cosentino et al, Curr Opin Infect Dis. 2023 Dec; 36(6): 564–571

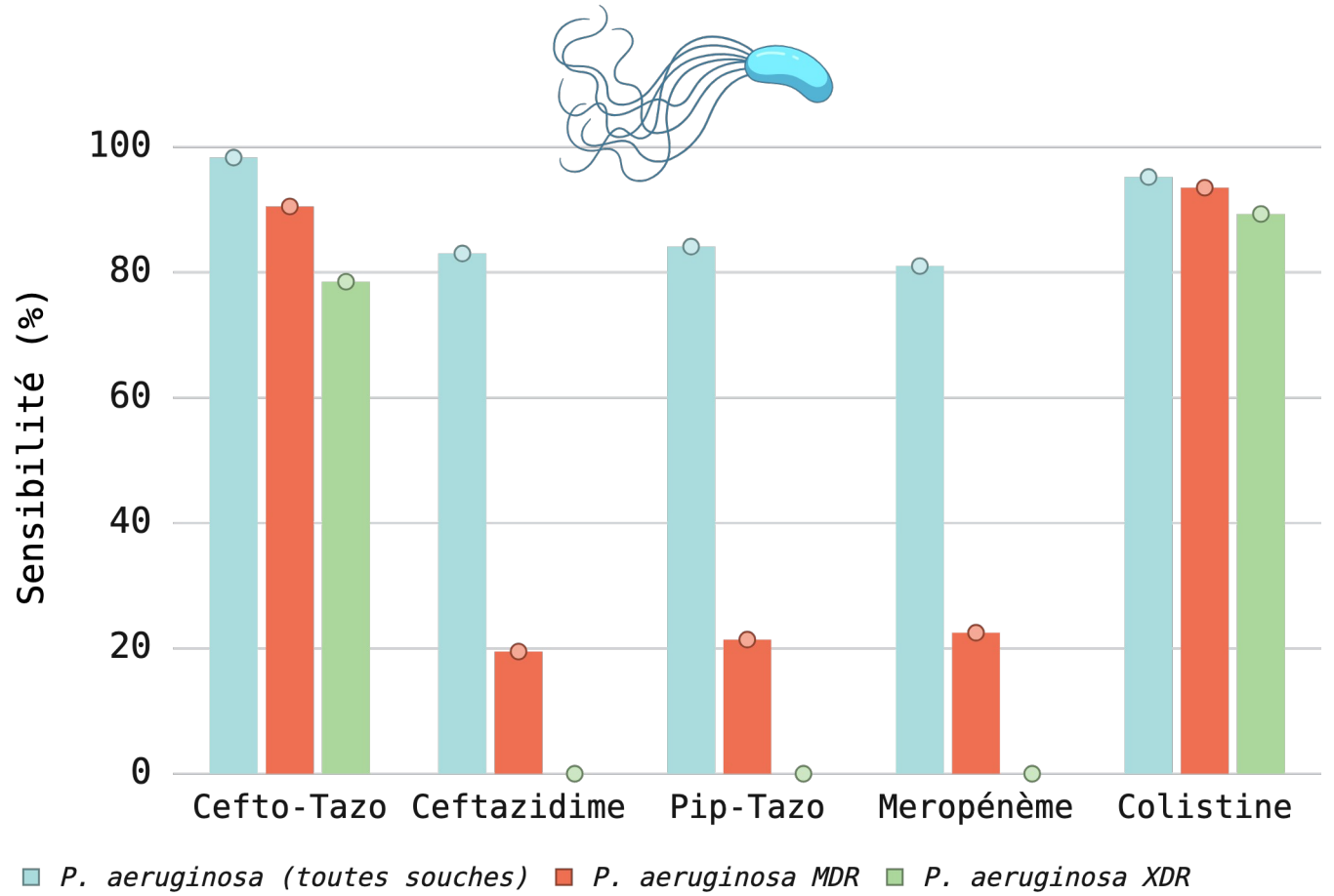
Sensibilité & nouvelles molécules





In vitro activity of **ceftolozane/tazobactam** versus antimicrobial non-susceptible *Pseudomonas aeruginosa* clinical isolates including MDR and XDR isolates obtained from across Canada as part of the CANWARD study, 2008–16

3229 *P. aeruginosa*



Walkty et al, J Antimicrob Chemother 2018; 73: 703

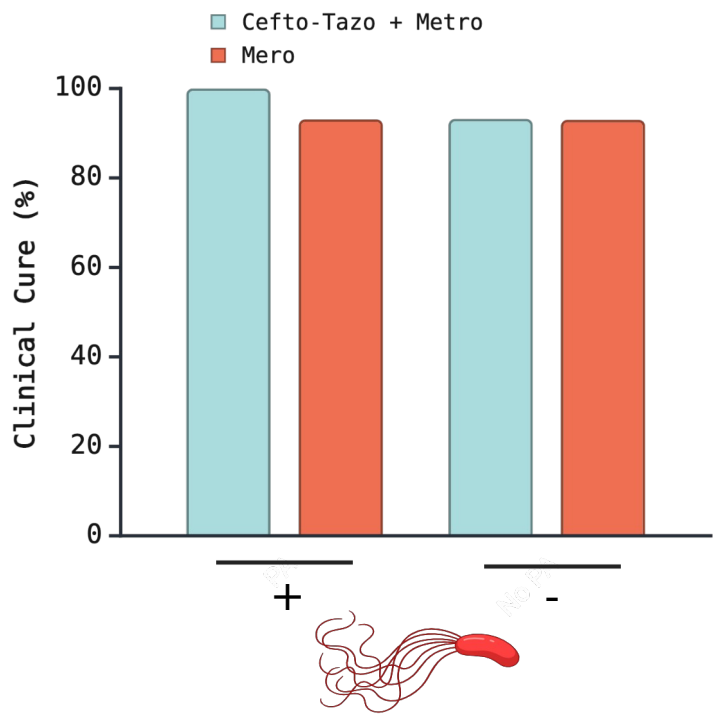
Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving *Pseudomonas aeruginosa* from a Randomized, Double-Blind, Phase 3 **Ceftolozane-Tazobactam** Study

- 806 patients
- Subgroup analysis
- ASPECT-cIAI trial

Cefto-Tazo + Métronidazole

Méropénème

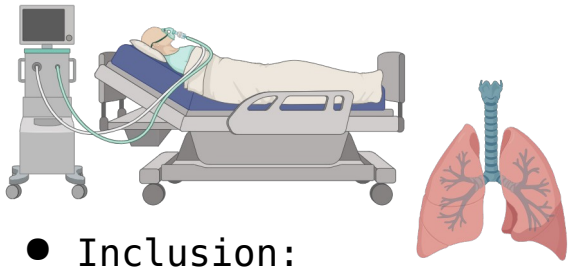
P. aeruginosa	+ (n=72)	• (n=734)
APACHE II <10	84.7%	81.2%
Appendice	59.7%	46.5%
Cholecystitis/ cholangitis	6.9%	18.9%
Stomach/ duodenum	5.6%	10.2%
Colon	23.6%	13.8%



Miller et al, AAC 2016, 60:4387

Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial

- Randomised, controlled, double-blind, non-inferiority trial
- 263 hospitals, 34 countries



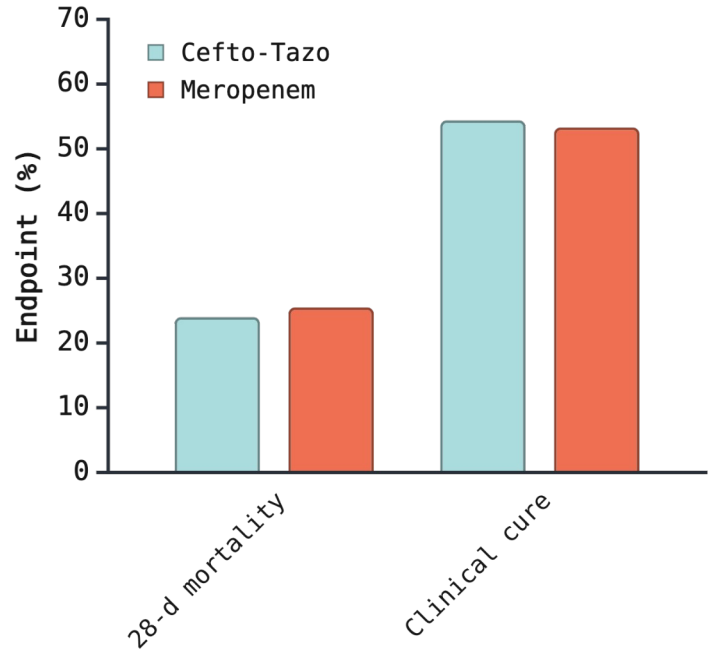
- Inclusion:
  - Mechanical ventilation
  - Nosocomial pneumonia

Ceftolozane–tazobactam (362)

Meropenem (364)

Primary endpoint

28-day all-cause mortality



Ceftolozane–tazobactam was non-inferior to meropenem in terms of both 28-day all-cause mortality and clinical cure at test of cure

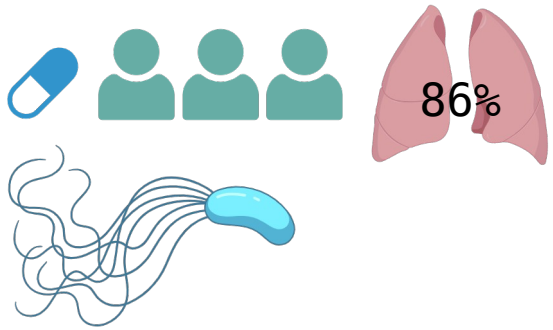
Kollef et al, Lancet Infect Dis 2019; 19: 1299–311

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

Pittsburgh Medical Center

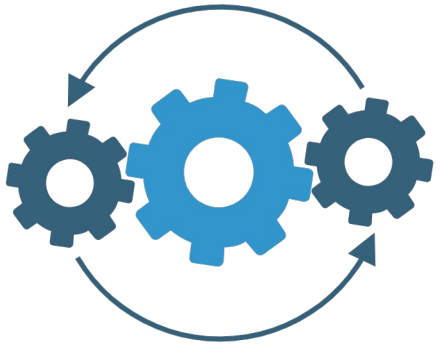
- June 2015-March 2016
- 21 patients

Ceftolozane–tazobactam



MDR-*P. aeruginosa*

Failure rate 29%
(6/21)



Resistance rate
14% (3/21)

AmpC overexpression

Haidar et al, Clinical Infectious Diseases 2017;65(1):110–20

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

- Retrospective, observational cohort study
- 6 centers

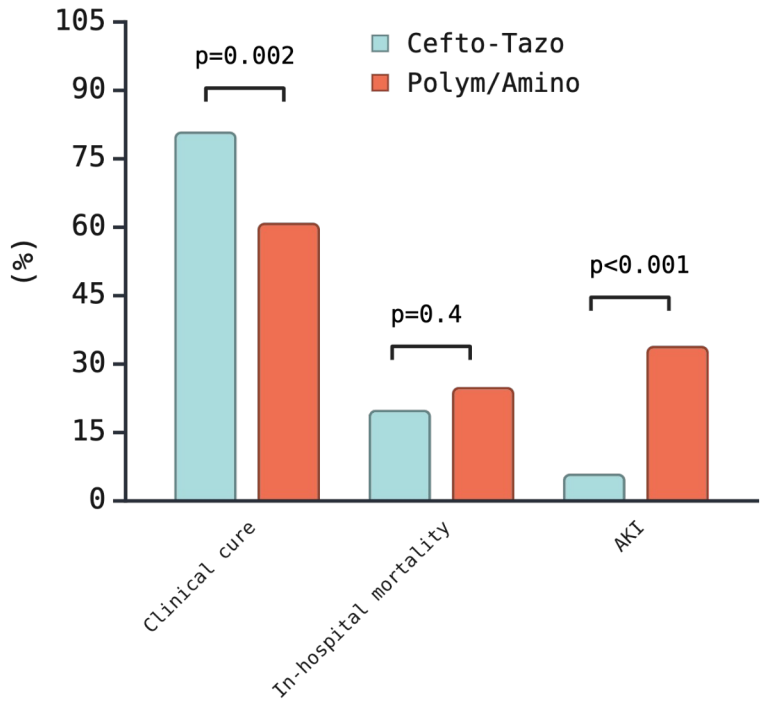
- MDR/XDR-*P. aeruginosa*

Ceftolozane–tazobactam (100)

Polymyxin/ Aminoglycoside (100)

Primary endpoint:

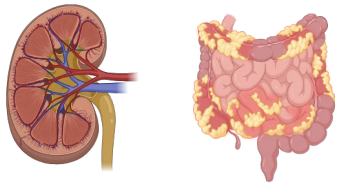
- Clinical cure
- Mortality
- AKI



Pogue et al, Clinical Infectious Diseases 2020;71(2):304–10

Ceftazidime-avibactam or best available therapy in patientswith ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (**REPRISE**):a randomised, pathogen-directed, phase 3 study

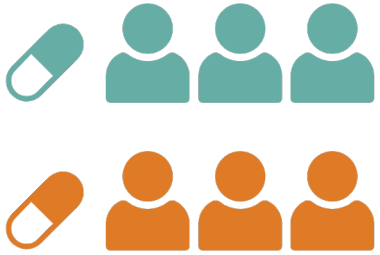
- Randomised, open-label trial
- 16 countries



Inclusion:

- Patients with cUTI or cIIA
- Infection due to ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa*

Ceftazidime – avibactam

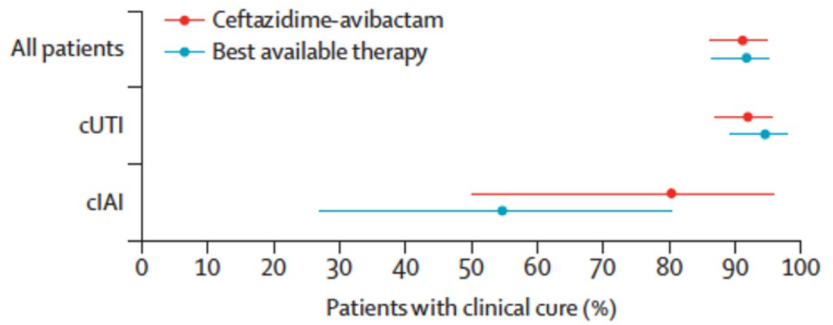


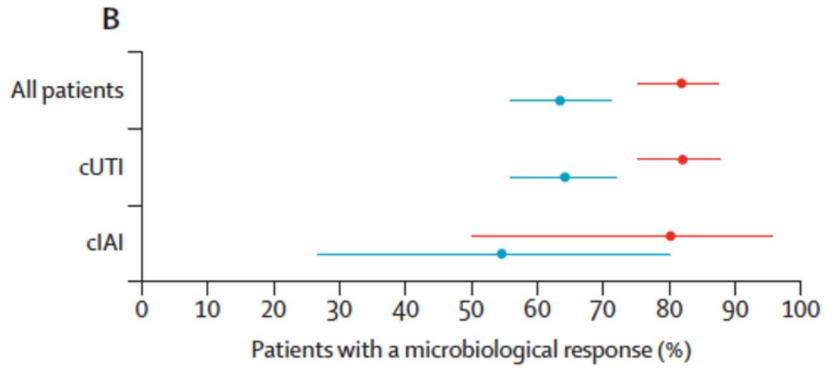
Best available therapy (Carbapenem 96%)

Primary endpoint

clinical response:

- at TOC visit
- 7-10 days after last infusion of study therapy



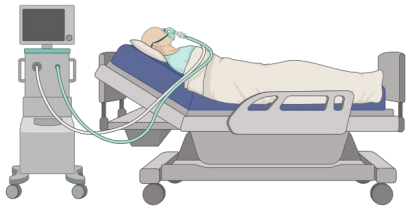


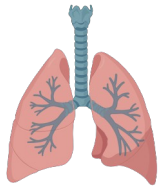
Ceftazidime-avibactam is a potential alternative to carbapenems in patients with ceftazidime-resistant Enterobacteriaceae and *P. aeruginosa*

Carmeli et al, Lancet inf Dis 2016, 16:661-73

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia(**REPROVE**): a randomised, double-blind, phase 3 non-inferiority trial

- Randomised, double blind trial
- 23 countries, 136 centres





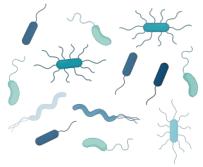
Inclusion:
- HAP & VAP

Ceftazidime–avibactam

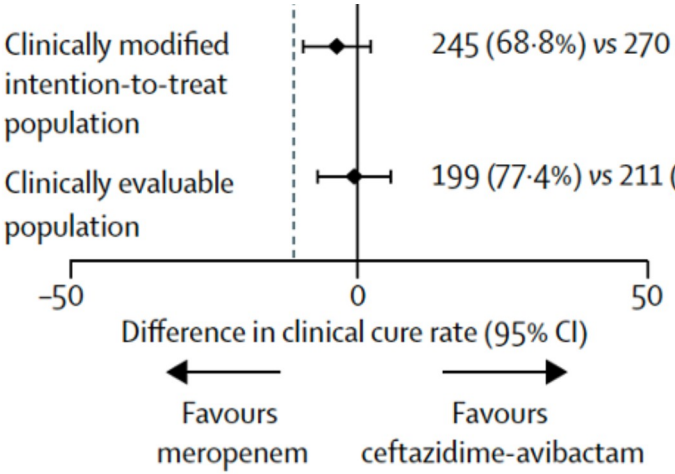
Meropenem

Primary endpoint:

Clinical cure at the test-of-cure visit (21–25 days after randomisation



- *Klebsiella pneumoniae* (37%)
- *Pseudomonas aeruginosa* (30%); 28% ceftazidime-non-susceptible



Ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia

Torres et al, Lancet Infect Dis 2018; 18: 285–95

Efficacy and safety of **ceftazidime/avibactam**: a systematic review and meta-analysis

- Systematic review and meta-analysis including RCTs evaluating ceftazidime/avibactam versus comparator for the treatment of any infection
- Primary outcome was 30 day all-cause mortality
- Seven publications (eight trials, 4093 patients) were included

Ceftazidime/avibactam ⇌ Comparator

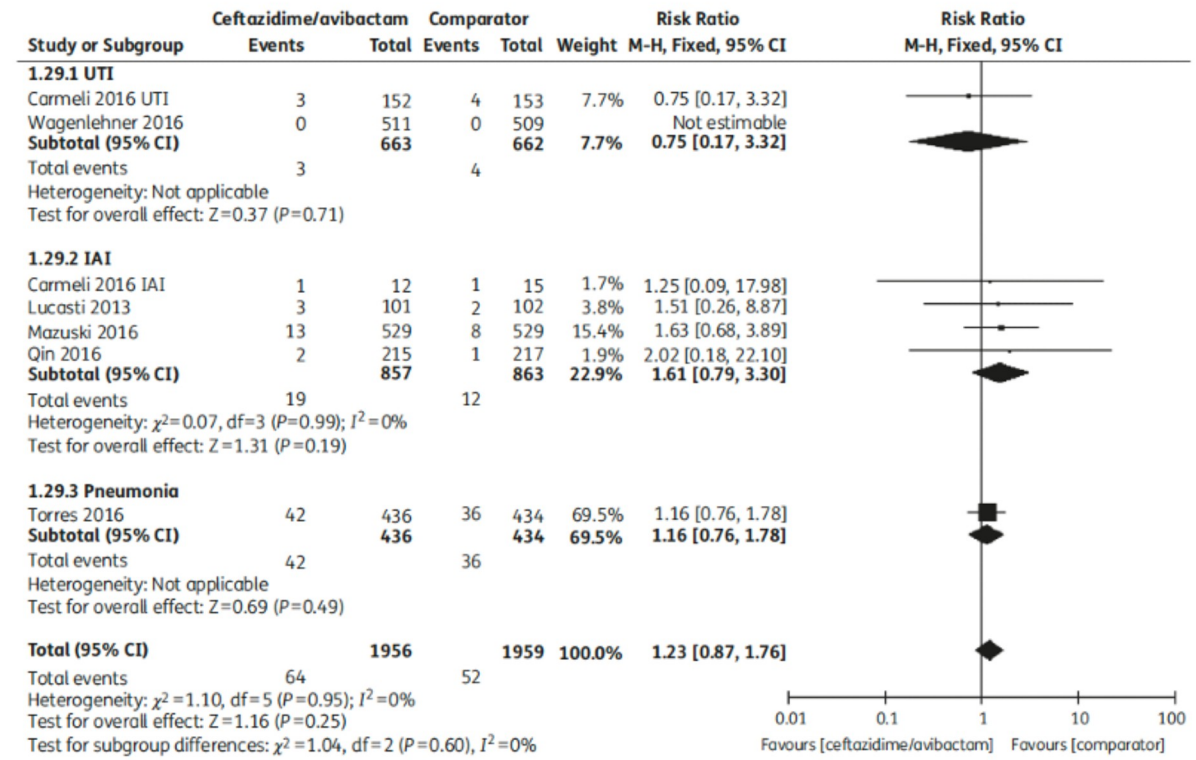
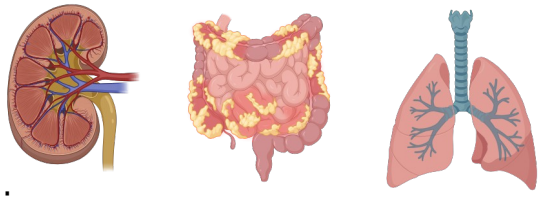


Figure 2. All-cause mortality at late follow-up. M-H, Mantel–Haenszel.

Sternbach et al, J Antimicrob Chemother 2018; 73: 2021–2029

Efficacy and safety of **ceftazidime/avibactam** in patients with infections caused by β-lactamase-producing Gram-negative pathogens:a pooled analysis from the Phase 3 clinical trial programme

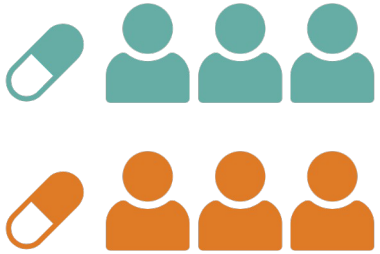
- Post-hoc analysis of 5 clinical trials



Inclusion:

- Patients with cUTI, cIIA, HAP
- Infection due β-lactamase-producing Gram-negative pathogens

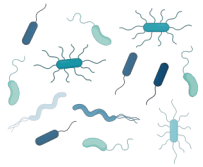
Ceftazidime–avibactam +/- Metro (1274)



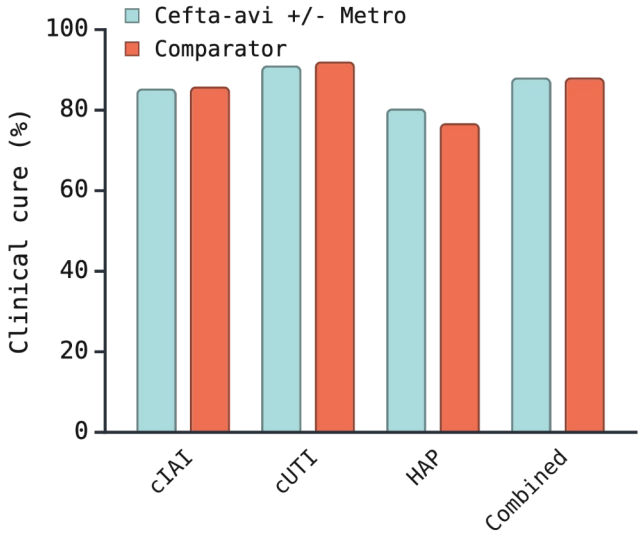
Best available therapy (1311)
(Carbapenem 97%)

Primary endpoint:

- Clinical cure
- Microbiological response



- *Escherichia coli* (n = 381),
- *Klebsiella pneumoniae* (n = 261)
- *Pseudomonas aeruginosa* (n = 53)



Efficacy and safety of ceftazidime/avibactam inpatients with infections caused by ESBLs, AmpC and serine carbapenemase-producing Gram-negative pathogens

Torres et al, J Antimicrob Chemother 2023; 78: 2672–2682

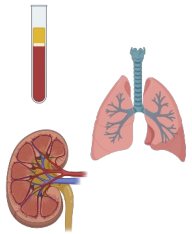
Colistin Versus **Ceftazidime-Avibactam** in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

- Prospective multicenter observational study

Inclusion:

- Patients with carbapenem-resistant enterobacterial infection

- Site
  - BSI 46% (63)
  - RTI 22% (30)
  - UTI 14% (19)



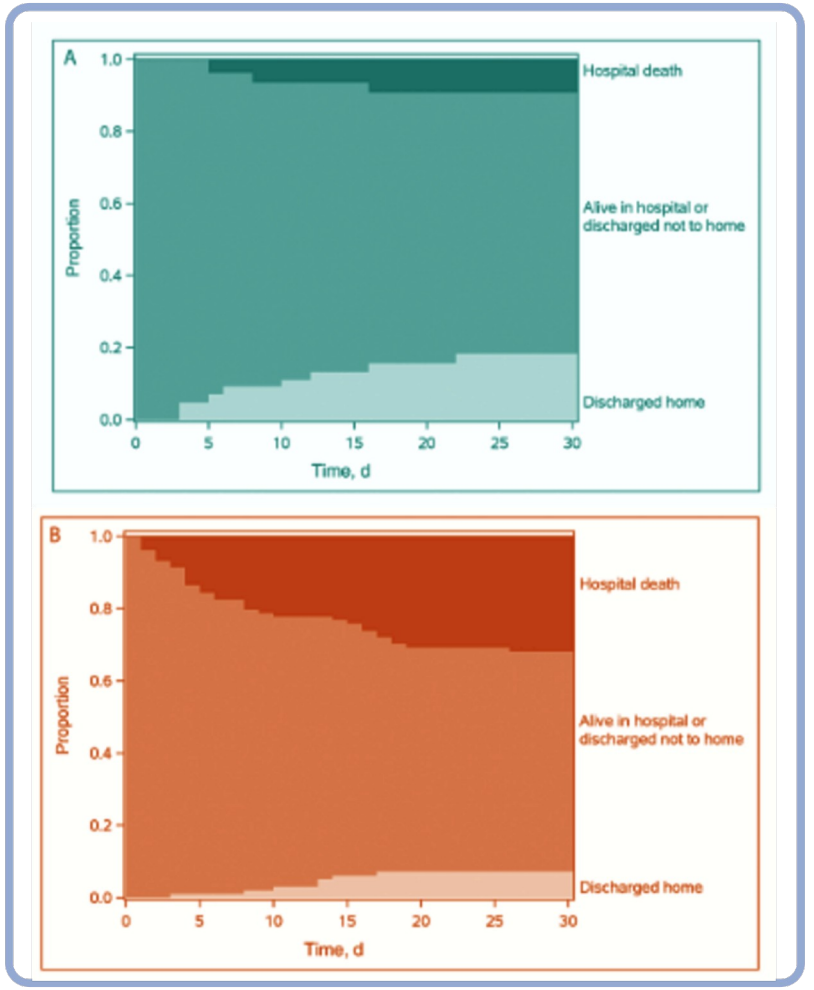
Ceftazidime–avibactam (38)

Colistin (99)

Primary endpoint:

- Efficacy
- Toxicity
- Benefit-risk

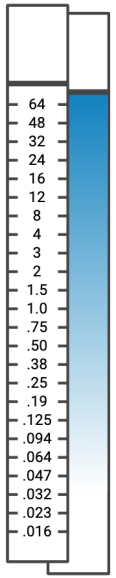
- Mortality at 30 days 9% vs 32%

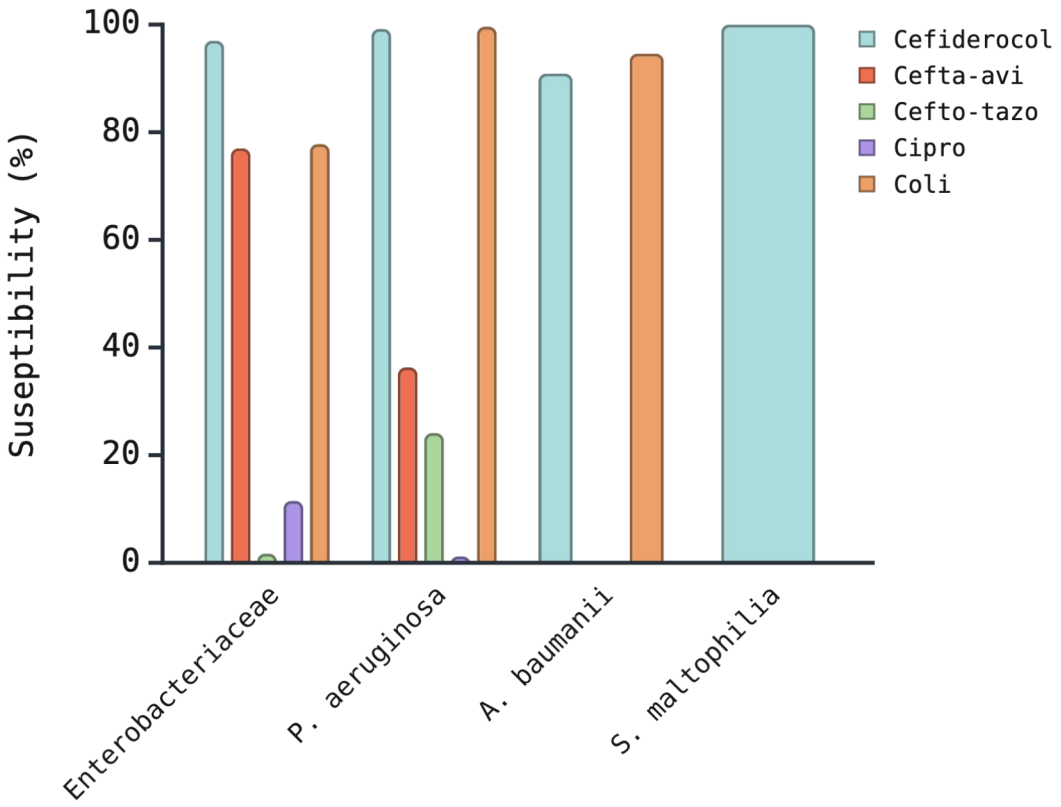


Van Duin et al, Clinical Infectious Diseases 2018;66(2):163–71

In Vitro Activity of **Cefiderocol** Against a Broad Range of Clinically Important Gram-negative Bacteria

Susceptibility Ratio to Cefiderocol and Comparators of Carbapenem-resistant Isolates From the SIDERO-CR-2014/2016 Study

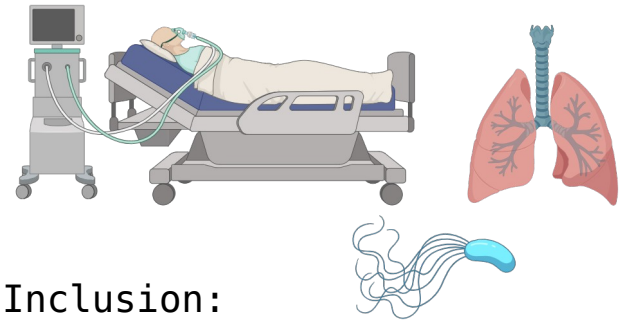




Yamano et al, Clinical Infectious Diseases 2019;69(S7):S544–51

Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial

- Randomised, double blind trial
- 17 countries, 76 centres



Inclusion:
- HAP & VAP
- Gram-negative pathogen

Cefiderocol

Meropenem

Primary endpoint:

All-cause mortality at day 14

	Cefi	Mero
K pneumoniae	33%	30%
P. aeruginosa	17%	16%
A baumanii	16%	16%
E coli	13%	15%
E clocae	5%	5%
ESBL	31%	29%
CarbaP	18.6%	13.6%

Clin cure

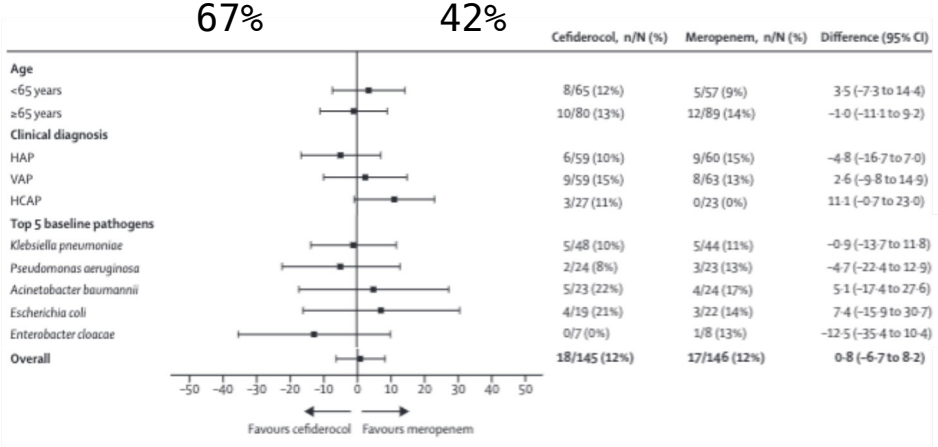
Microb eradic

65%

41%

67%

42%



All-cause mortality at day 14

Cefiderocol was non-inferior to meropenem in the treatment of Gram-negative nosocomial pneumonia

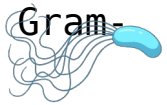
Wunderik et al, Lancet Infect Dis 2021; 21: 213–25

Efficacy and safety of **cefiderocol** or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

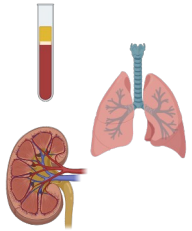
- Randomized (2/1) open label
- 95 hospitals, 16 countries

Inclusion:

- Carbapenem-resistant Gram-negative



- Site
  - BSI 31% (37)
  - RTI 50% (59)
  - UTI 19% (22)

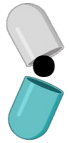


Cefiderocol (80)

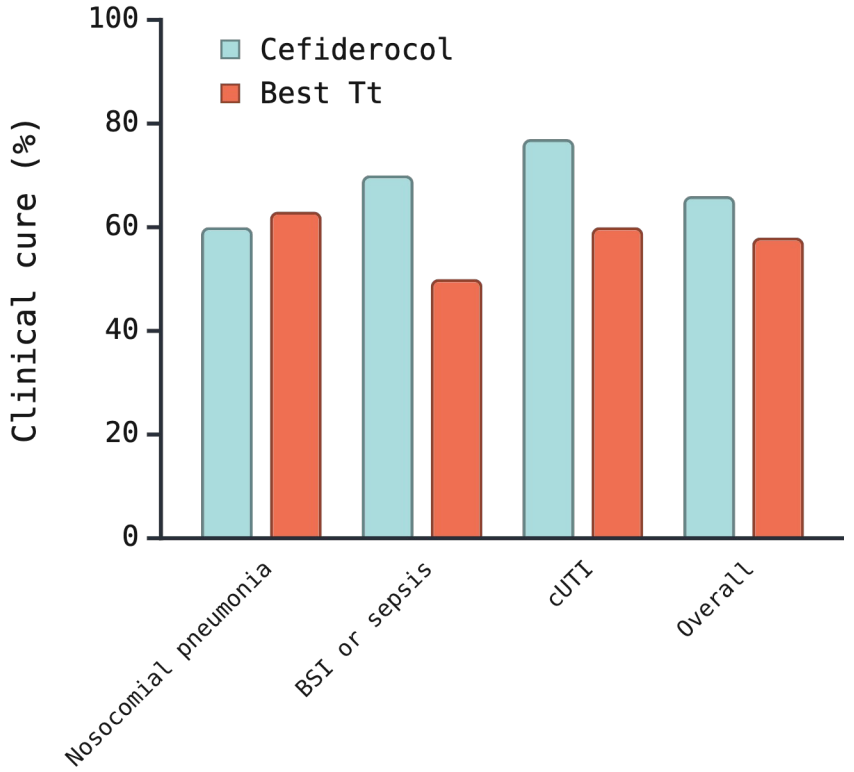
Best available (38)

Primary endpoint:

- Clinical cure at day 7
- Microbiological eradication for UTIs



- Cefiderocol: 83% monotherapy vs. 28%
- Best treatment: Colistin-based 66%

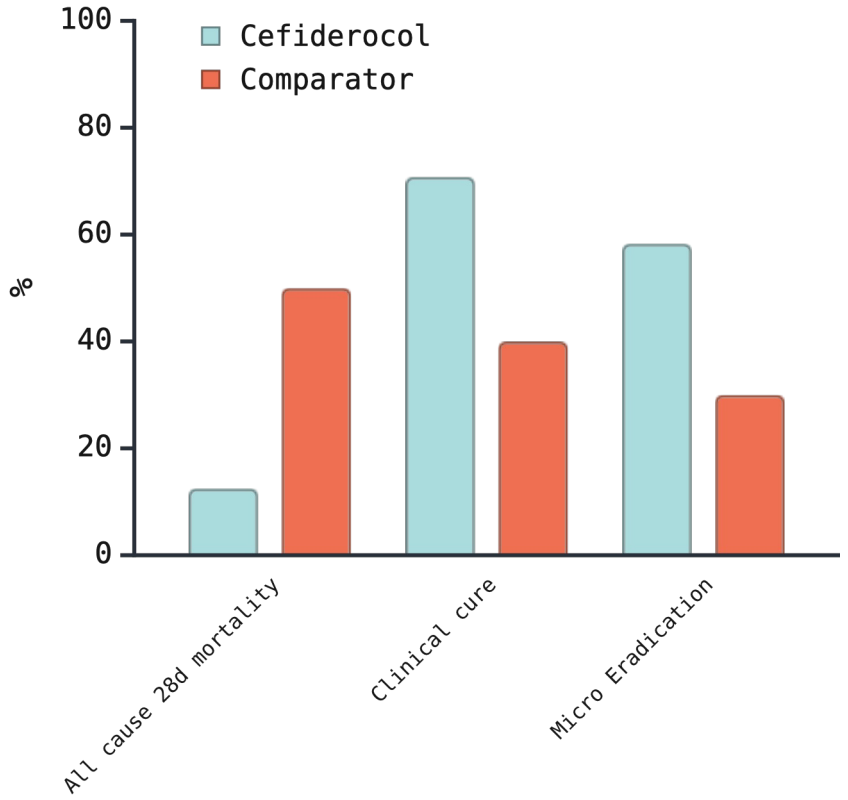


Cefiderocol had similar clinical and microbiological efficacy to best available therapy

Bassetti et al, Lancet Infect Dis 2021; 21: 226–40

Cefiderocol for the Treatment of Infections Due To Metallo-Beta-Lactamase-Producing Pathogens in the CREDIBLE-CR And APEKS-NP Phase 3 Randomized Studies

- **CREDIBLE-CR study:** Open-label, descriptive (A MultiCenter, RandomizED, Open-label ClInical Study of S-649266 or Best AvailabLE Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-negative Pathogens
- **APEKS-NP study:** Noninferiority Acinetobacter, *Pseudomonas,Escherichia coli, Klebsiella, Stenotrophomonas* - nosocomial pneumonia , critically ill patients with Gram-negative nosocomial pneumonia
- Patient-level information on MBL-producing bacterial infections



In the CREDIBLE-CR and APEKS-NP studies, cefiderocol treatment was effective against Gram-negative bacteria producing metallo-B-lactamases;

Timsit et al, Clinical Infectious Diseases 2022, 75(6):1081-4

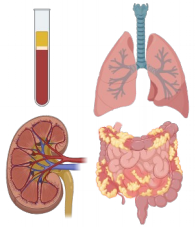
Effect and Safety of **Meropenem–Vaborbactam** versus Best-Available Therapy in Patientswith Carbapenem-Resistant *Enterobacteriaceae* Infections: The TANGO II Randomized Clinical Trial

- Phase 3, multinational, open-label, randomized controlled trial 2014 to 2017

Inclusion:

- Patients with carbapenem-resistant enterobacterial infection

- Site
  - BSI 46.8% (22)
  - RTI 10.6% (5)
  - UTI 34% (16)
  - cIAI 8.5% (4)

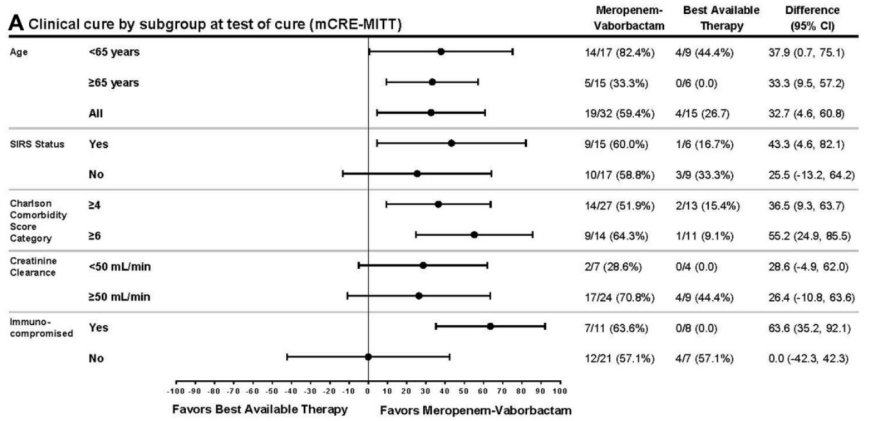


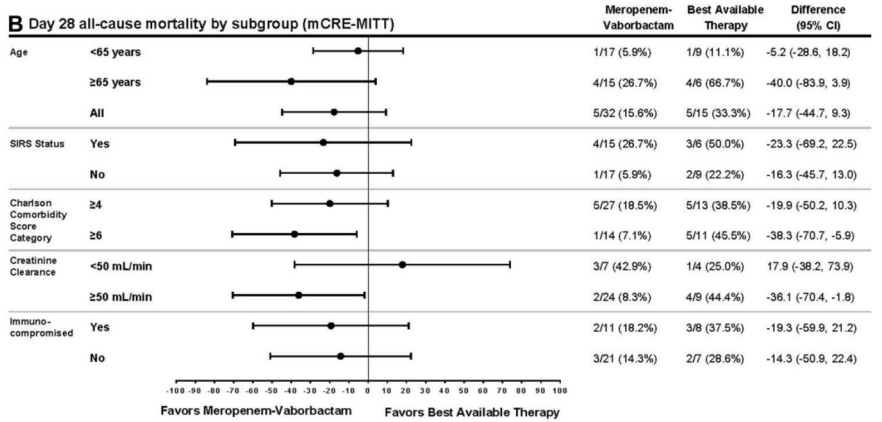
Mero-Vabor (32)

Best available treatment (15)

Primary endpoint:

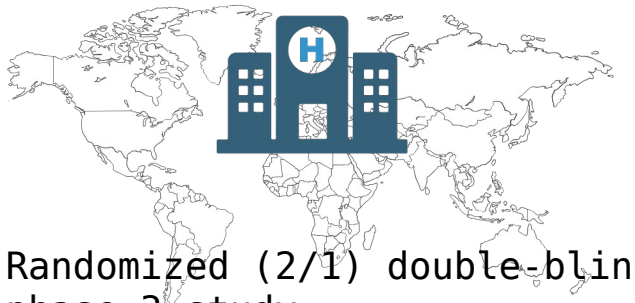
- Clinical cure
- Microbiological cure
- Benefit-risk
- Mortality at 28 days





Wunderink et al, Infect Dis Ther (2018) 7:439–455

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of **Imipenem/ Cilastatin /Relebactam** vs Colistin Plus Imipenem in Patients With Imipenem-non susceptible Bacterial Infections

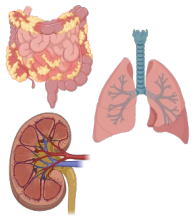


- Randomized (2/1) double-blind phase 3 study
- 35 hospitals, 17 countries

Inclusion:

- IMP-resistant pathogen (but IMP-RLB sensitive)

- Site
  - IIA 31% (37)
  - RTI 50% (59)
  - UTI 19% (22)



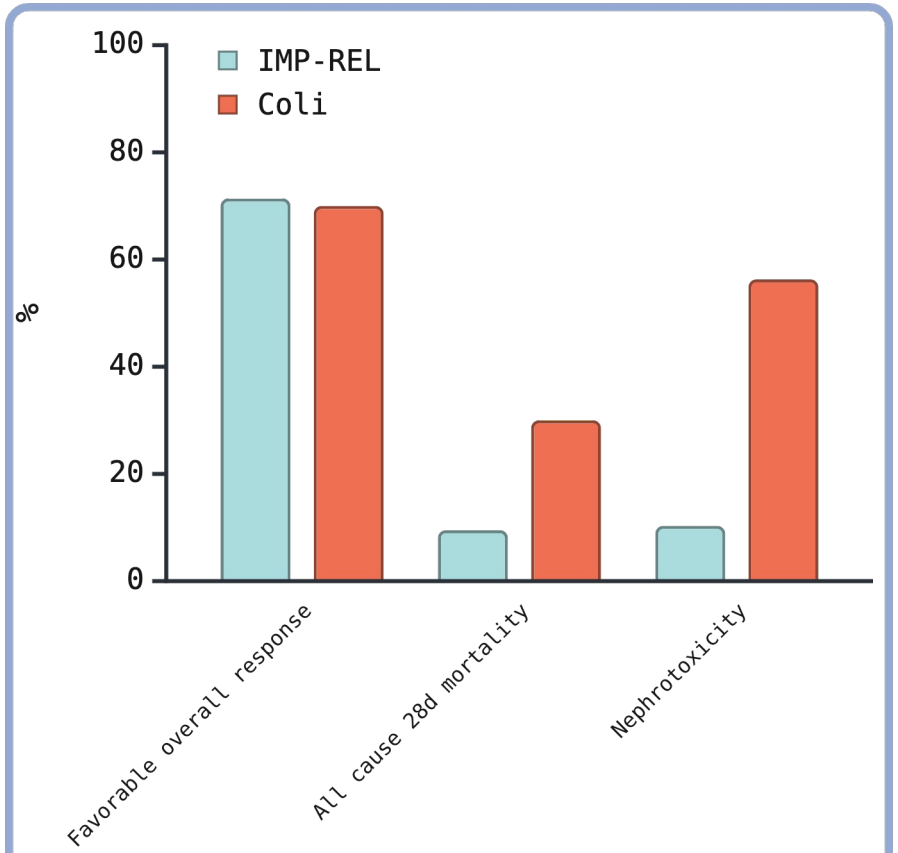
IMP-RLB (21)

Colistin (10)

Primary endpoint:

- Favorable overall response

	IMP-RLB	Coli
C. freundii	0%	*4.8%*
E. cloacae	0%	*4.8%*
K oxytoca	16%	16%
K pneumoniae	14.3%	10%
P. aeruginosa	*76.2%*	80%
Class A	25	
Class C	26	
Class D	1	

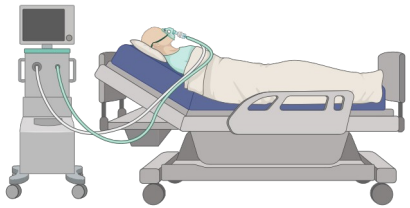


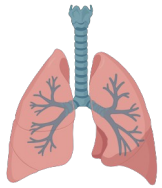
Imipenem/relebactam is an efficacious and well-tolerated treatment option

Motsch et al, Clinical Infectious Diseases 2020;70(9):1799–808

A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of **Imipenem/Cilastatin/Relebactam** Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

- Randomised, double blind trial
- 27 countries, 113 centres





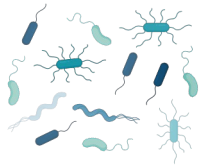
Inclusion:
- HAP & VAP

IMP-REL (264)

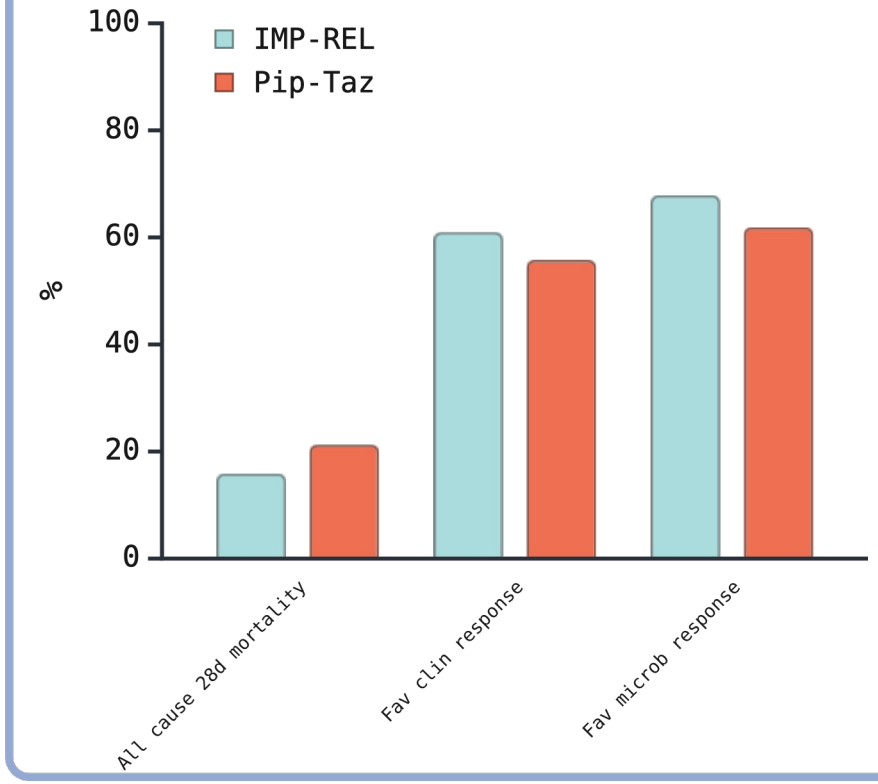
Pip-Tazo (267)

Primary endpoint:

Day 28 all-cause mortality



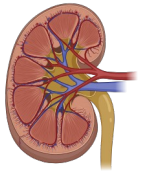
- *Klebsiella pneumoniae* (25.6%)
- *Pseudomonas aeruginosa* (18.9%)



Titov et al, Clin Infect Dis 2020 Aug 12;ciaa803.

Cefepime–Taniborbactam in Complicated Urinary Tract Infection

- Double-blind, double-dummy,randomized, active-controlled trial
- 2/1 ratio
- 15 countries, 68 sites



Inclusion:

- Patients with cUTI

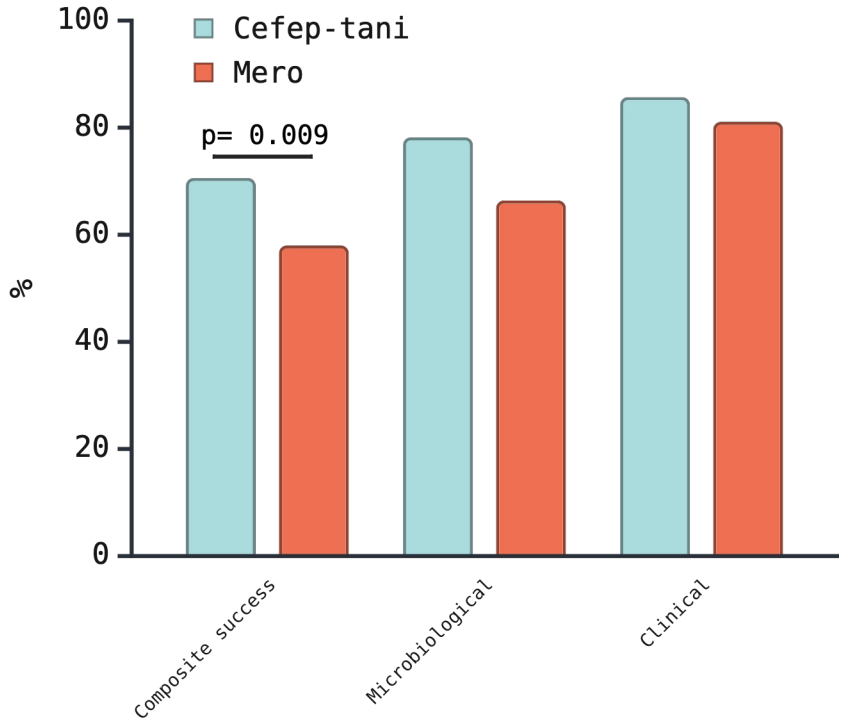
Cefepime-taniborbactam (293)

Meropenem (143

Primary endpoint

Microbiologic and Clinical success (composite success)

	Cefep-tab	IMP
Cefep-R	*22.5%*	21%
ESBL	*25.9%*	28%
MDR	*34.1%*	38.5%



Cefepime–taniborbactam was superior to meropenem for the treatment of compli-cated UTI that included acute pyelonephritis

Wagenlehner et al, N Engl J Med 2024;390:611-22

Cefta-R, IMP-R

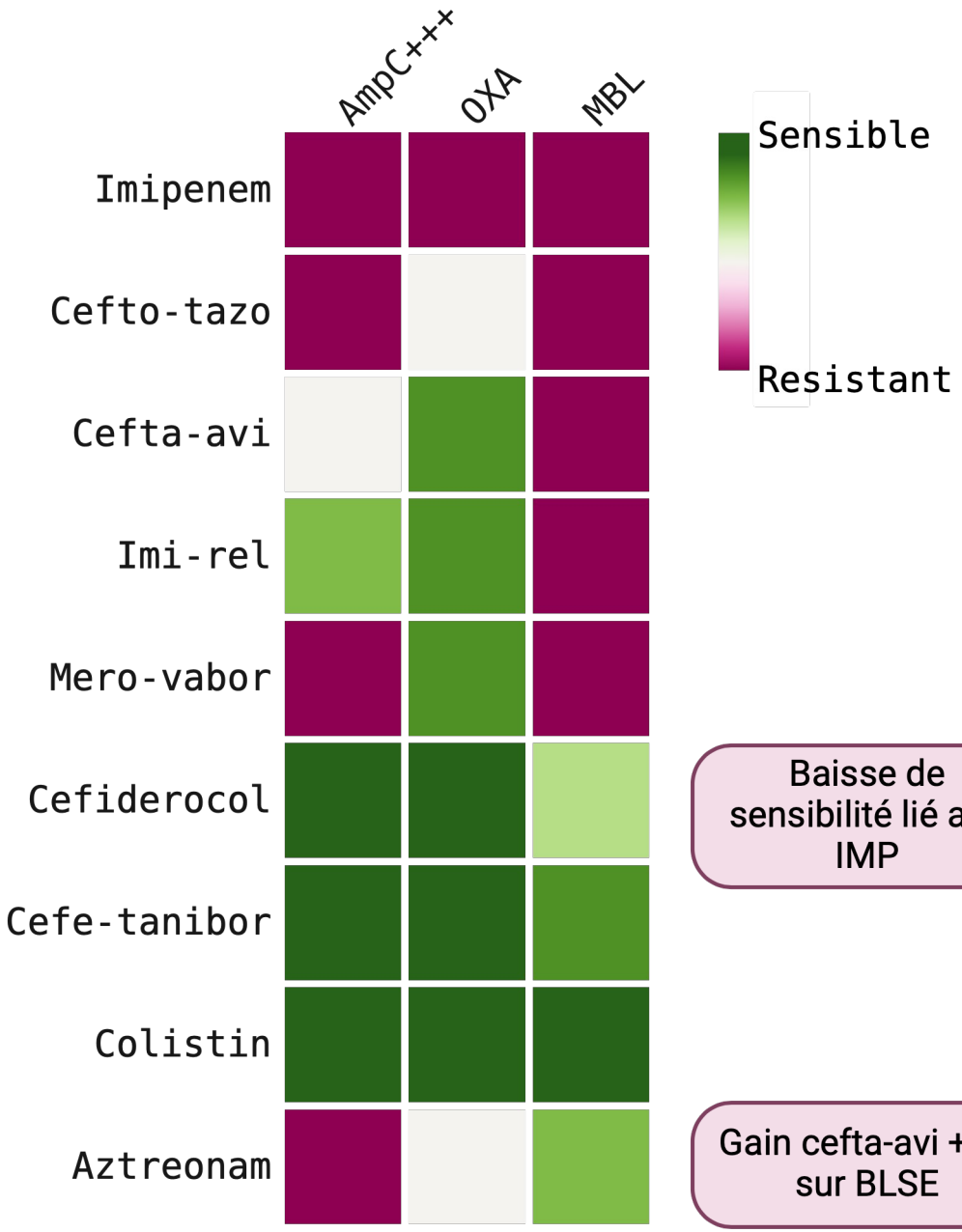
AmpC, OXA-48, KPC

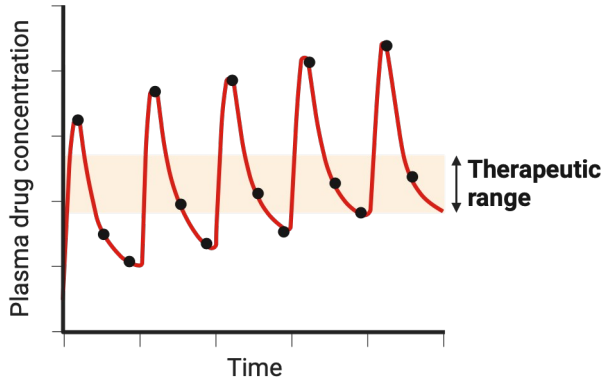
AmpC, OXA

KPC, OXA

AmpC, CP

AmpC, OXA, MBL

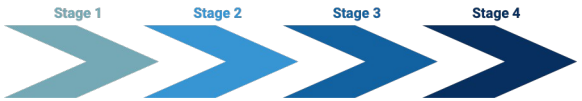




Baisse de sensibilité lié aux IMP

Gain cefta-avi + az sur BLSE

Dans le pipeline:



- Céfépime-zidebactam
- Aztreonam-avibactam
- Meropeneme-nacubactam

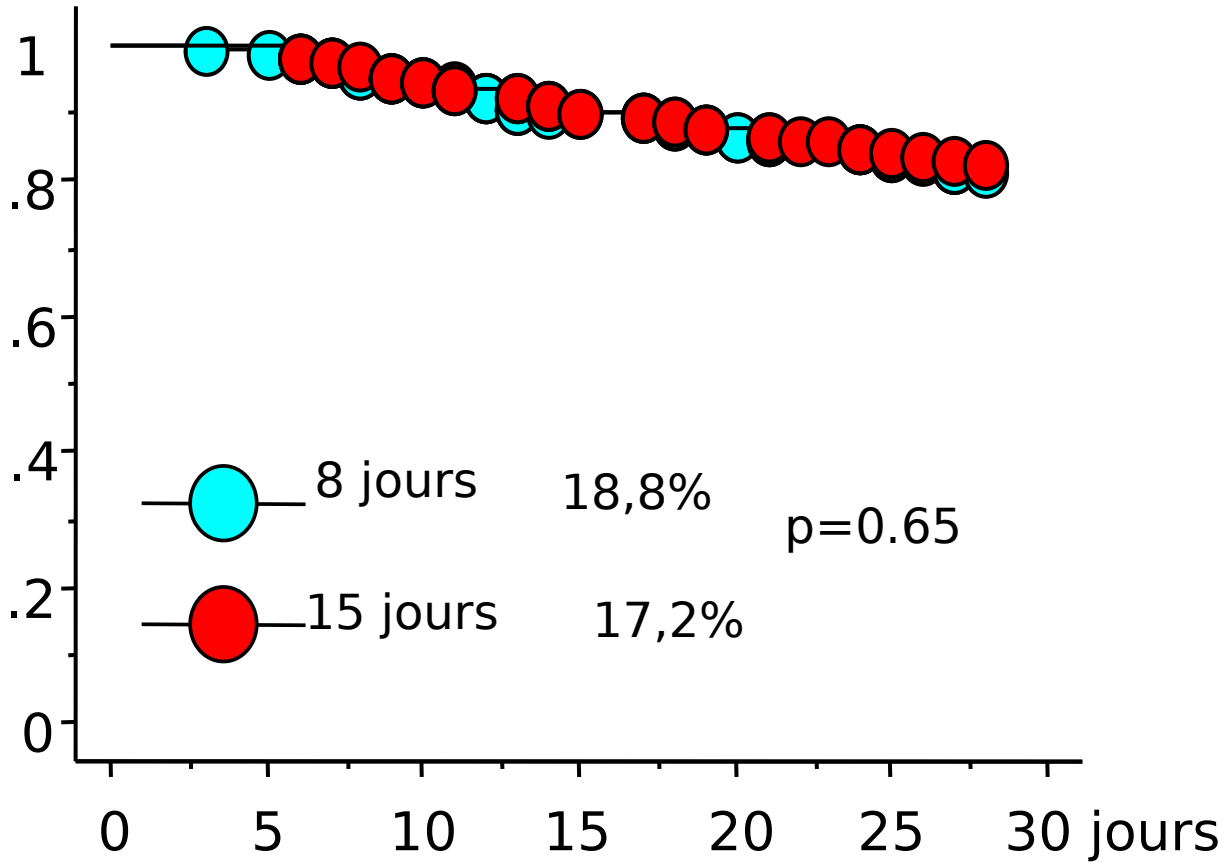
Plan

- ✓ Sensibilité & PK/PD
- ✓ EUCAST…..
- ✓ Nouvelles molécules
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

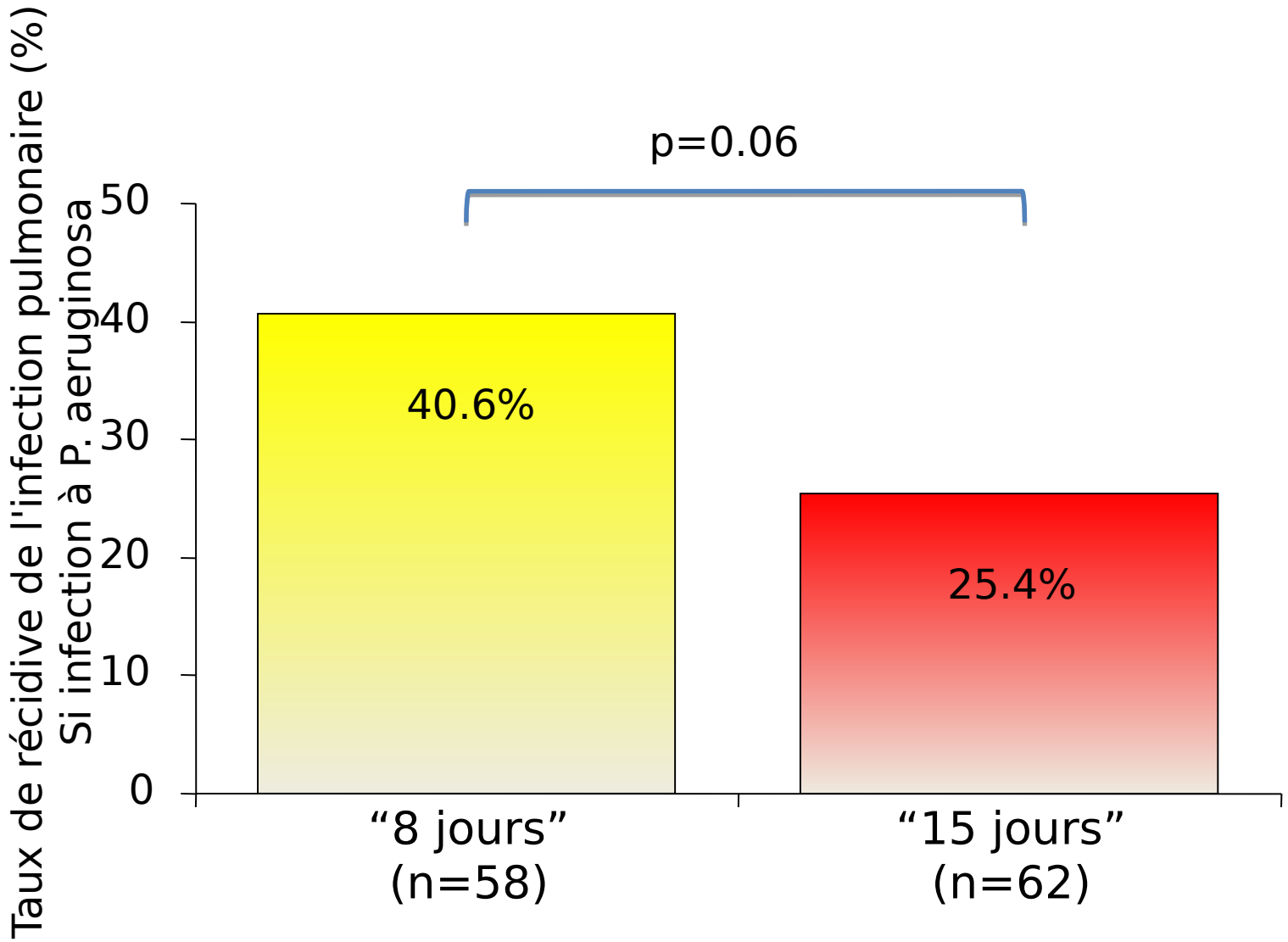
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

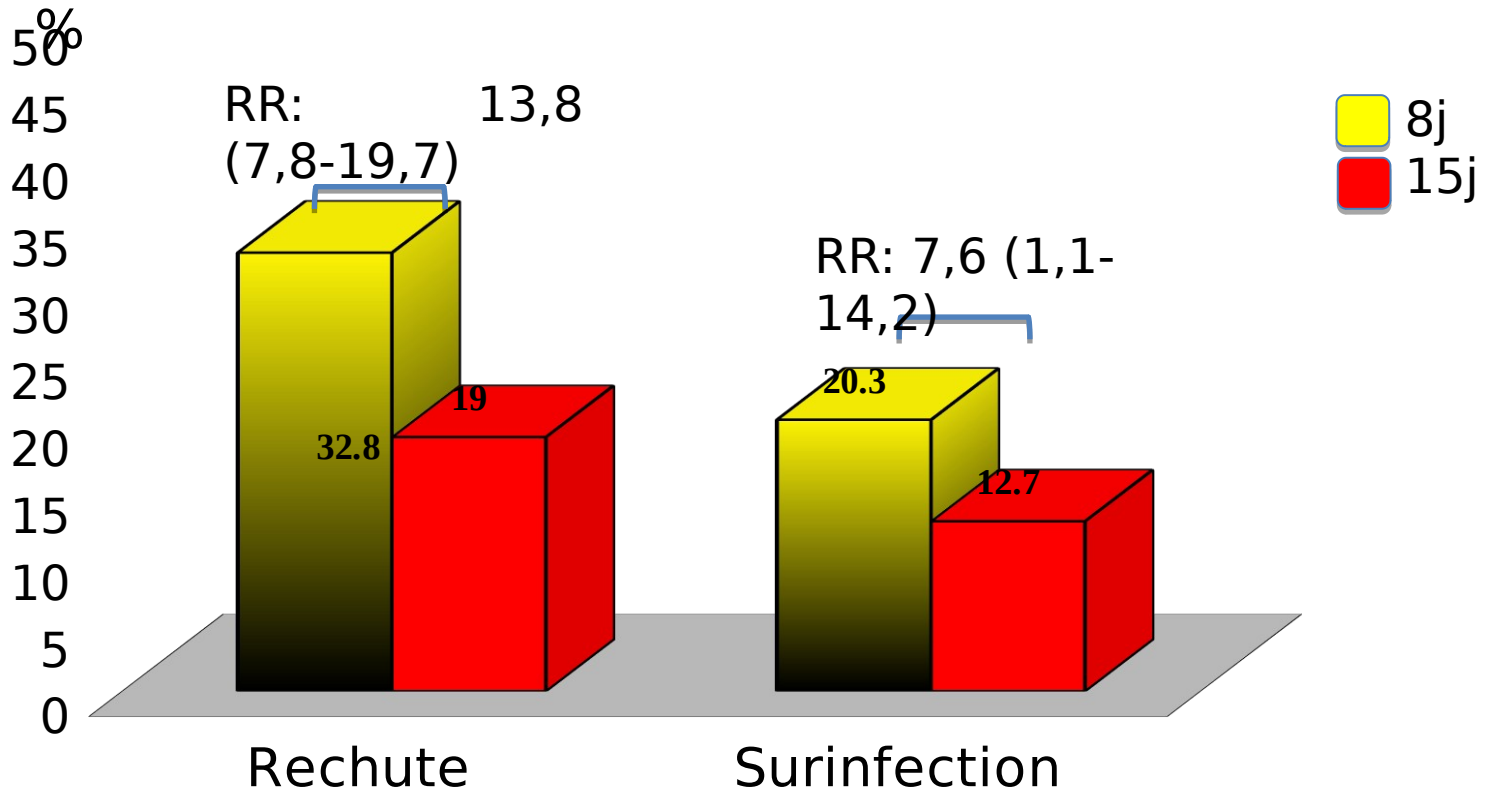
Jean Chastre, MD
Michel Wolff, MD
Jean-Yves Fagon, MD
Sylvie Chevret, MD
Franck Thomas, MD
Delphine Wermert, MD
Eva Clementi, MD
Jesus Gonzalez, MD
Dominique Jusserand, MD
Pierre Asfar, MD
Dominique Perrin, MD
Fabienne Fieux, MD
Sylvie Aubas, MD
for the PneumA Trial Group



Chastre et al, JAMA 200



Chastre et al, JAMA 200



Chastre et al, JAMA 200

Comparison of 8 versus 15 days of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial

- ✓ Nationwide, randomized, open-labeled, multicenter, non-inferiority trial
- ✓ PA-VAP
  - Short-duration treatment (8 days)
  - Long-duration treatment (15 days).
- ✓ Composite endpoint combining
  - Mortality and PA-VAP recurrence rate
  - During hospitalization in the ICU within 90 days.

- ✓ Non-inferiority of 8-day group compared to the 15-day group was not demonstrated
- ✓ However, the lack of power limits the interpretation of this study.

Table 2 Primary outcome and its components, according to study group

Outcome or event	15-day group (*N* = 98)	8-day group (*N* = 88)	Difference (90% CI)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in ITT population—no. (%)	25/98 (25.5)	31/88 (35.2)	9.7% (− 1.9–21.2%)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in PP population—no. (%)	22/80 (27.5)	29/72 (40.3)	12.8% (− 0.4–25.6%)
PA-VAP recurrence rate during hospitalization in the ICU in ITT population—no. (%)	9/98 (9.2)	15/88 (17)	7.9% (− 0.5–16.8%)

PA-VAP, pseudomonas aeruginosa ventilator-associated pneumonia; ICU, Intensive Care Unit; PP, per protocol; ITT, intention-to-treat

Table 3 Secondary outcomes, according to study group

Outcome or event	15-day group (*N* = 98)	8-day group (*N* = 88)	Difference (95% CI)
Duration of mechanical ventilation, days[a]	25 (15.5–35)	22 (12–41)	− 3 (− 9 to 5)
Duration of ICU stay, days	34 (23–56)	34 (20–54)	0 (− 7 to 6)
Exposure to antibiotics during ICU stay, days	23 (15–34)	18 (11.5–28.5)	− 5 (− 9 to 0)
Number of extra pulmonary infections during ICU stay[a]	1 (0–2)	1 (0–2)	0 (− 1 to 1)
Acquisition of MDR pathogens during ICU stay—no. (%)	24/97 (24.7)	17/84 (20.2)	− 4.5% (− 16.8 to 8.3%)

Data are no. (%) or median (IQR)

ICU, intensive care unit; MDR, multidrug-resistant

[a] Data available: *n* = 96 in "15-day" group, *n* = 84 in "8-day" group

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Bouglé et al, Intensive Care Med. 2022 Jul;48(7):841-

Antibiotic Therapy for *Pseudomonas aeruginosa* Bloodstream Infections: How Long Is Long Enough?

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Faculty of Biology and Medicine

- ✓ Multicenter, observational, propensity-score–weighted cohort
  - 249 adults
  - uncomplicated *Pseudomonas aeruginosa* bacteremia,
- ✓ Treatment duration
  - Short-course: median 9 days (interquartile range [IQR], 8–10)
  - Long course: median 16 days (IQR, 14–17).
- ✓ Results: similar odds of recurrent infection or death within 30 days

Fabre et al, Clinical Infectious Diseases 2019;69(11):201

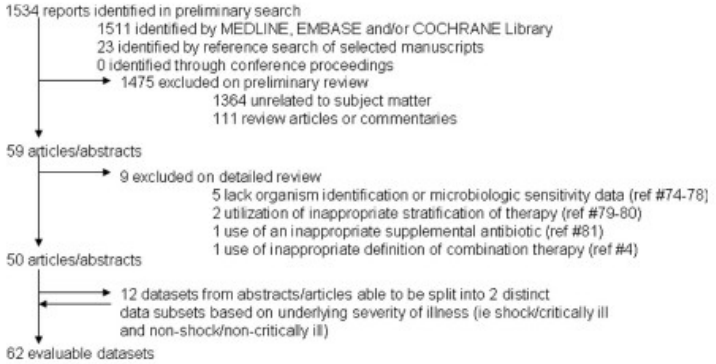
Plan

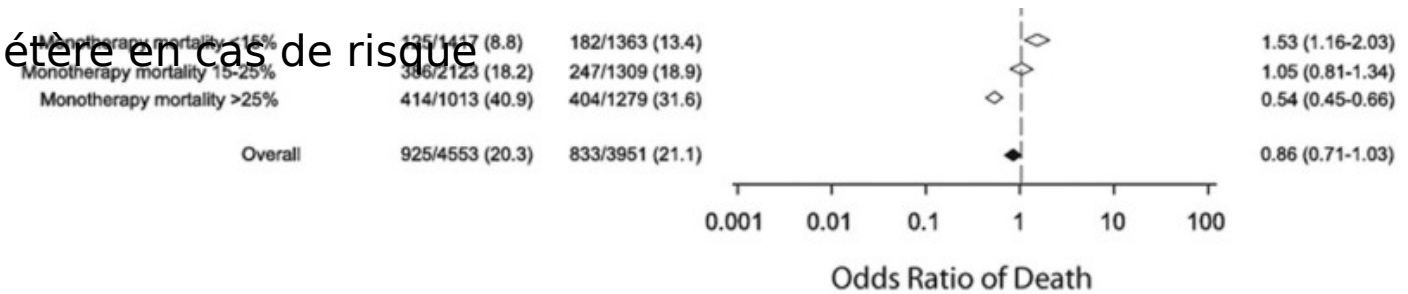
- ✓ Sensibilité & PK/PD
- ✓ EUCAST…..
- ✓ Nouvelles molécules
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

- ✓ Etudes randomisées ou observationnelles d'infections sévères potentiellement associées à un sepsis ou un choc septique
- ✓ 50 études conformes aux critères de sélection
- ✓ 62 dataset évaluables

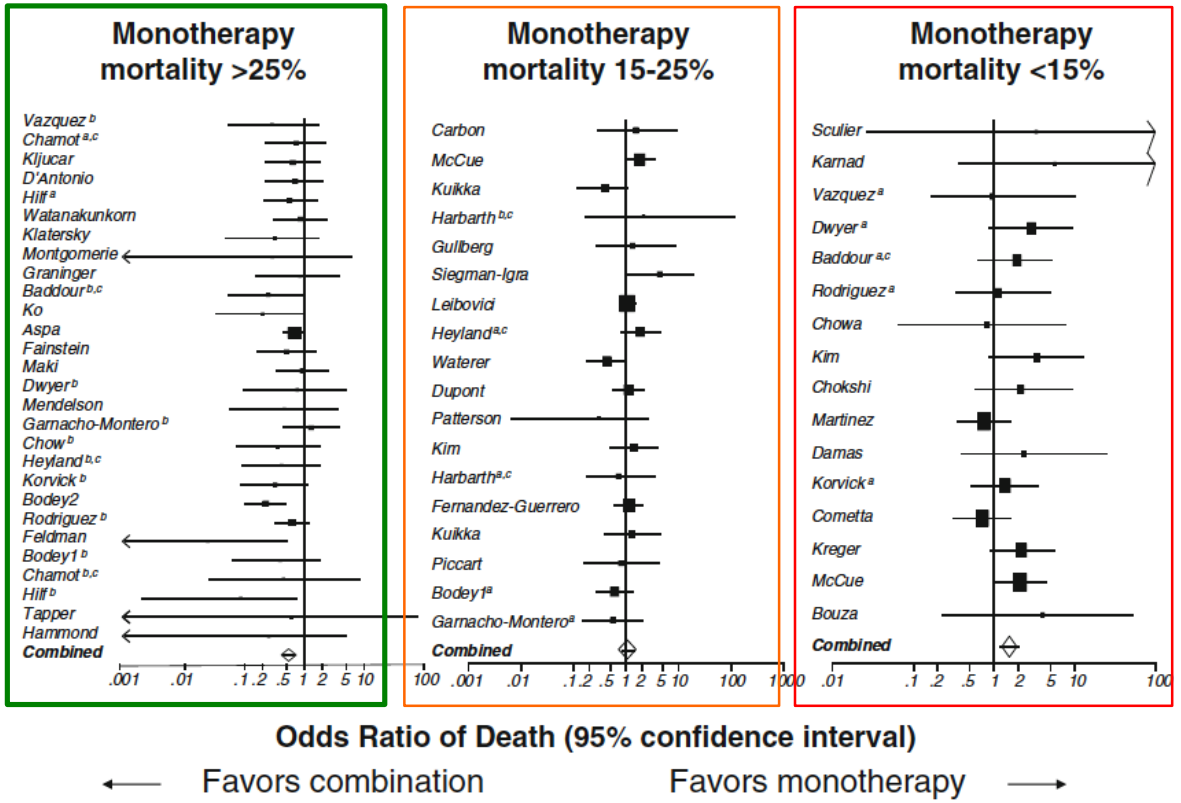
- ✓ Pas de bénéfice global sur cette « population »
- ✓ Bénéfice uniquement dans le sous groupe avec un risque de mortalité >25%
- ✓ Potentiellement délétère en cas de risque <15%





Kumar et al, Crit Care Med 2010,

Combination and severity



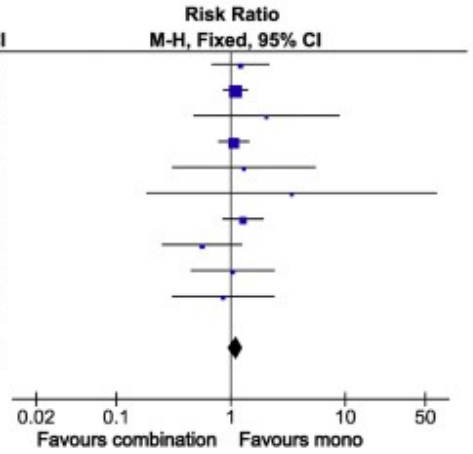
Liang Curr Infect Dis Rep 2015

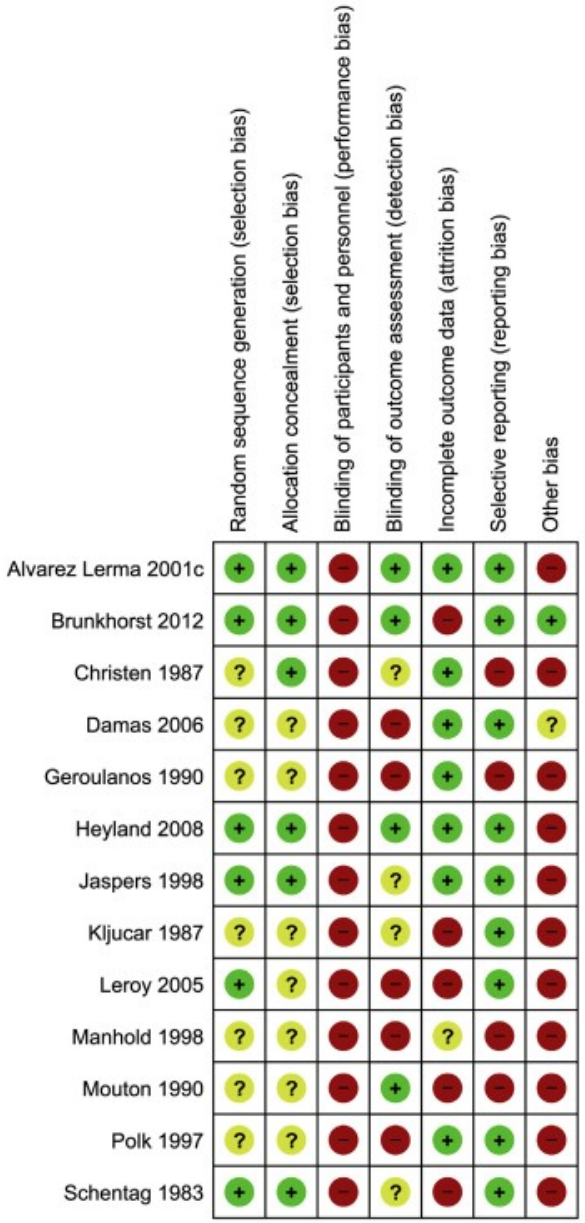
Empirical mono- versus combination antibiotic therapy in adult intensive care patients with severe sepsis – A systematic review with meta-analysis and trial sequential analysis

- ✓ 30 RCT (2633 patients) inclus
- ✓ Comparaison mono vs association
- ✓ Patients adultes avec un sepsis sévère

Study or Subgroup	Combination therapy Events	Total	Mono therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alvarez Lerma 2001c	20	71	16	69	6.8%	1.21 [0.69, 2.14]
Brunkhorst 2012	96	272	84	262	36.0%	1.10 [0.87, 1.40]
Damas 2006	8	39	2	20	1.1%	2.05 [0.48, 8.77]
Heyland 2008	71	369	67	370	28.1%	1.06 [0.79, 1.44]
Jaspers 1998	4	40	3	39	1.3%	1.30 [0.31, 5.43]
Kljucar 1987	3	34	0	16	0.3%	3.40 [0.19, 62.16]
Leroy 2005	45	201	34	194	14.6%	1.28 [0.86, 1.90]
Manhold 1998	6	23	13	28	4.9%	0.56 [0.25, 1.24]
Polk 1997	10	63	9	59	3.9%	1.04 [0.45, 2.38]
Schentag 1983	6	49	7	49	2.9%	0.86 [0.31, 2.37]
Total (95% CI)		**1161**		**1106**	**100.0%**	**1.11 [0.95, 1.29]**
Total events	269		235			

Heterogeneity: Chi² = 5.05, df = 9 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)





Sjövall et al, Journal of Infection (2017) 74, 331e3

Question: Should empirical combination vs. mono antibiotic therapy be used in adult ICU patients with severe sepsis and septic shock?

Bibliography: Sjövall et al. Empirical combination versus mono antibiotic therapy in adult intensive care care patients with severe sepsis and septic shock - a systematic review with meta-analysis and trial sequential analysis of randomised controlled trials

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With empirical mono therapy	With empirical combination therapy		Risk with mono therapy	Risk difference with combination therapy (95% CI)
Motality at longest follow-up (CRITICAL OUTCOME)											
2266 (11 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias strongly suspected[3]	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision, publication bias	235/1105 (21.3%)	269/1161 (23.2%)	**RR 1.1** (0.95 to 1.29)	**Study population**	
										213 per 1000	**21 more per 1000** (from 11 fewer to 62 more)
										Moderate	
											-

Pas de différence entre les patients présentant un APACHE II >20/<20

Sjövall et al, Journal of Infection (2017) 74, 331e

Kumar vs Sjövall

- ✓ Inclusion des études observationnelles
- ✓ Pas de différence empirique et documenté
- ✓ Etudes intégrées s'étalant sur 36 ans
- ✓ Outcome primaire de substitution augmente l'effet traitement de 40 à 50% (biomarqueurs, biochimie, imagerie, …)(BMJ 2013;346:f457)
- ✓ Absence d'évaluation du risque d'erreur (type I et II)
- ✓ Non exhaustif au niveau des études publiées

- ✓ Le bénéfice de l'association ne semble être présent que si celle-ci comporte une pénicilline à spectre étroit, sans activité anti-*P. aeruginosa*
- ✓ Perte d'effet si monothérapie avec un large spectre

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Faculty of Biology and Medicine

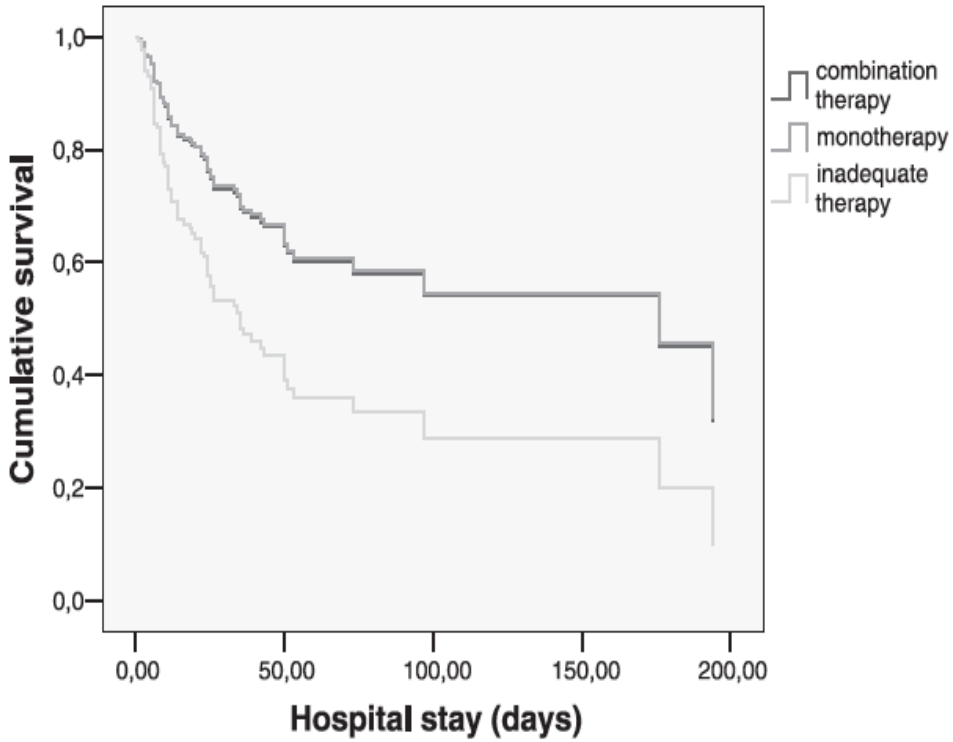
ETUDES CLINIQUES PAVM

canton de vaud

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

183 épisodes de VAP à *P. aeruginosa*

Tt final	Survivants n=106	Décédés n=77
APACHE II	18.7	19.8
Choc septique	38 (35.8)	52 (67.5)
Monothérapie	22 (19.9)	12 (15.6)
Association	84 (81.1)	60 (84.4)



Garnacho-Montero et al, Crit Care Med 2007

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

Table 5. Variables independently associated with mortality using Cox proportional regression analysis

	aHR	95% CI	*p*
Age	1.02	1.01–1.04	.005
Chronic cardiac failure	1.90	1.04–3.47	.035
Effective empirical therapy			.02
Combined therapy	1		
Monotherapy	0.90	0.50–1.63	.73
Inappropriate therapy	1.85	1.07–3.10	.02

aHR, adjusted hazard ratio; CI, confidence interval.

Garnacho-Montero et al, Crit Care Med 2007

Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials

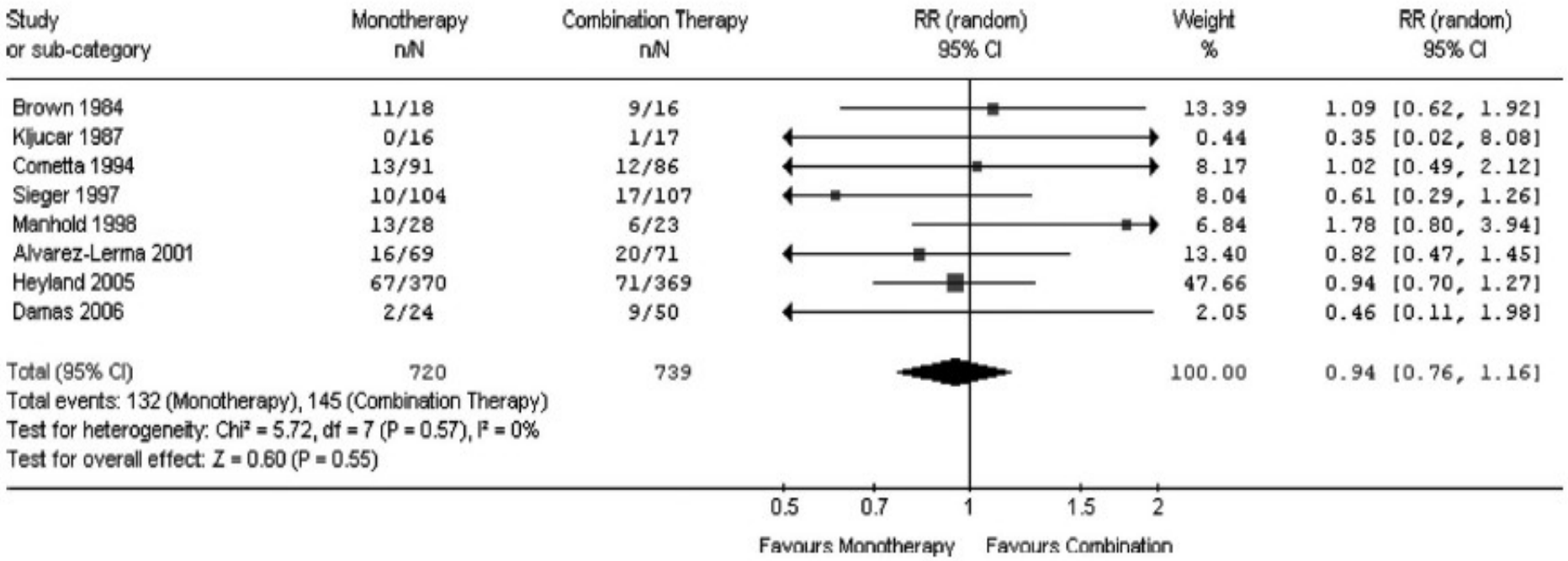
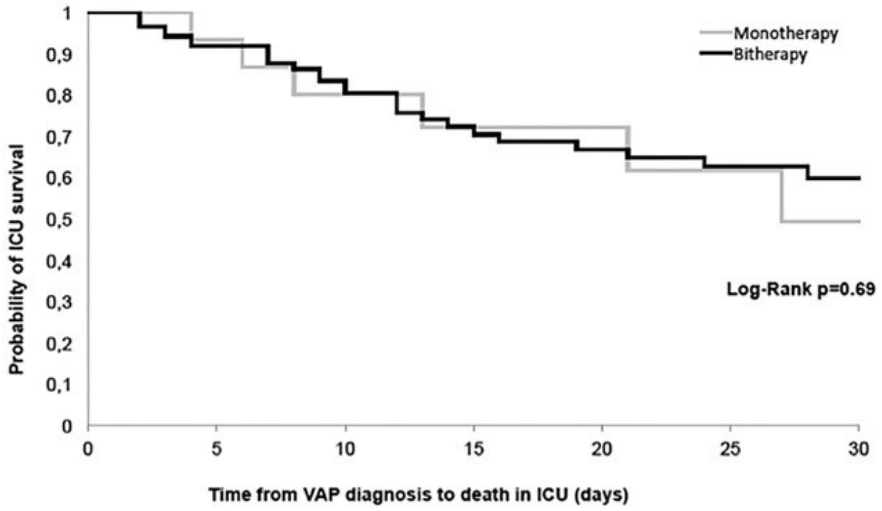


Figure 4. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. *RR*, relative risk; *CI*, confidence interval.

Aarts et al, Crit Care Med 2008

- ✓ Etude rétrospective de cohorte 1994-2014
  - 100 patients: 85 associations/15 monothérapie, 9 inadequates
  - SAPS 2: 46, 45% choc, Colonisation 60%, Multi-R 31%
  - Mortalité associée (HR)
    - SAPS>40: 3.08
    - Choc: 4.71



- ✓ L'association augmente la probabilité d'antibiothérapie appropriée sans impact sur la mortalité

Deconinck et al, Infection 2017, 49:3

Association between combination antibiotic therapy as opposed as monotherapy and outcomes of ICU patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia: an ancillary study of the iDIAPASON trial

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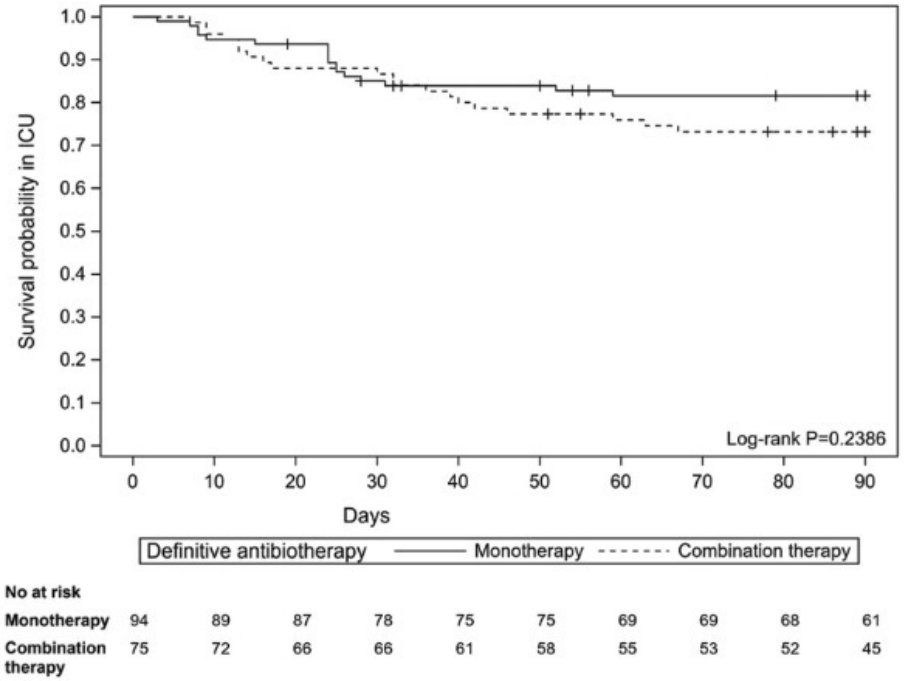
- ✓ 169 Patients with PA-VAP randomized in the iDIAPASON trial (short-duration—8 days vs. long-duration—15 days)
  - Received appropriate antibiotic therapy
- ✓ Results
  - 37 patients (21.9%) died
    - 17 received monotherapy
    - 20 received a combination therapy (P = 0.180).
  - Similar for
    - Recurrence rate of VAP
    - Number of extra pulmonary infections
    - Acquisition of multidrug-resistant (MDR) bacteria during the ICU stay
- ✓ Monotherapy versus combination therapy.
- ✓ The primary outcome was the mortality rate at day 90.

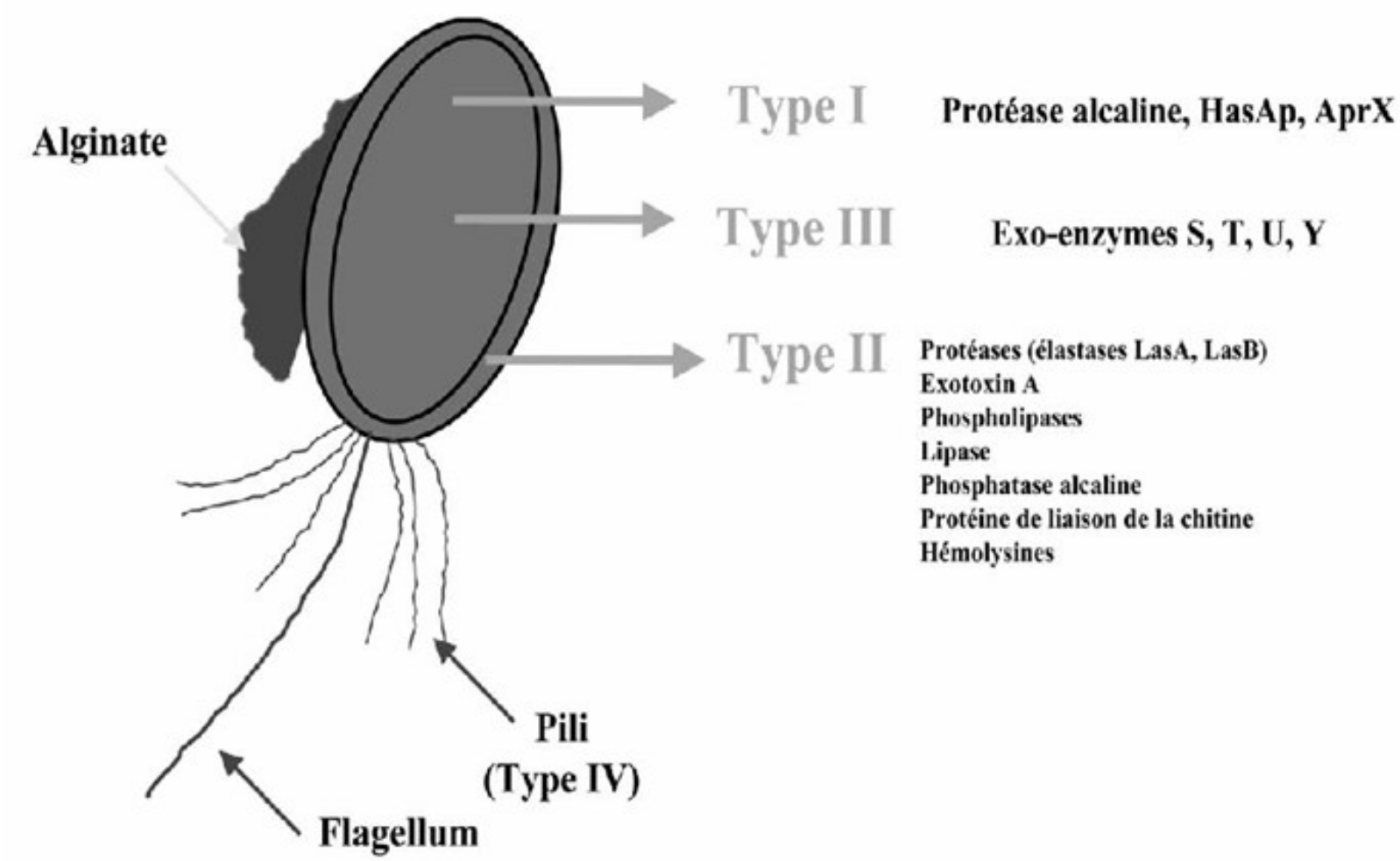


Foucrier et al. Critical Care (2023) 27:2

Plan

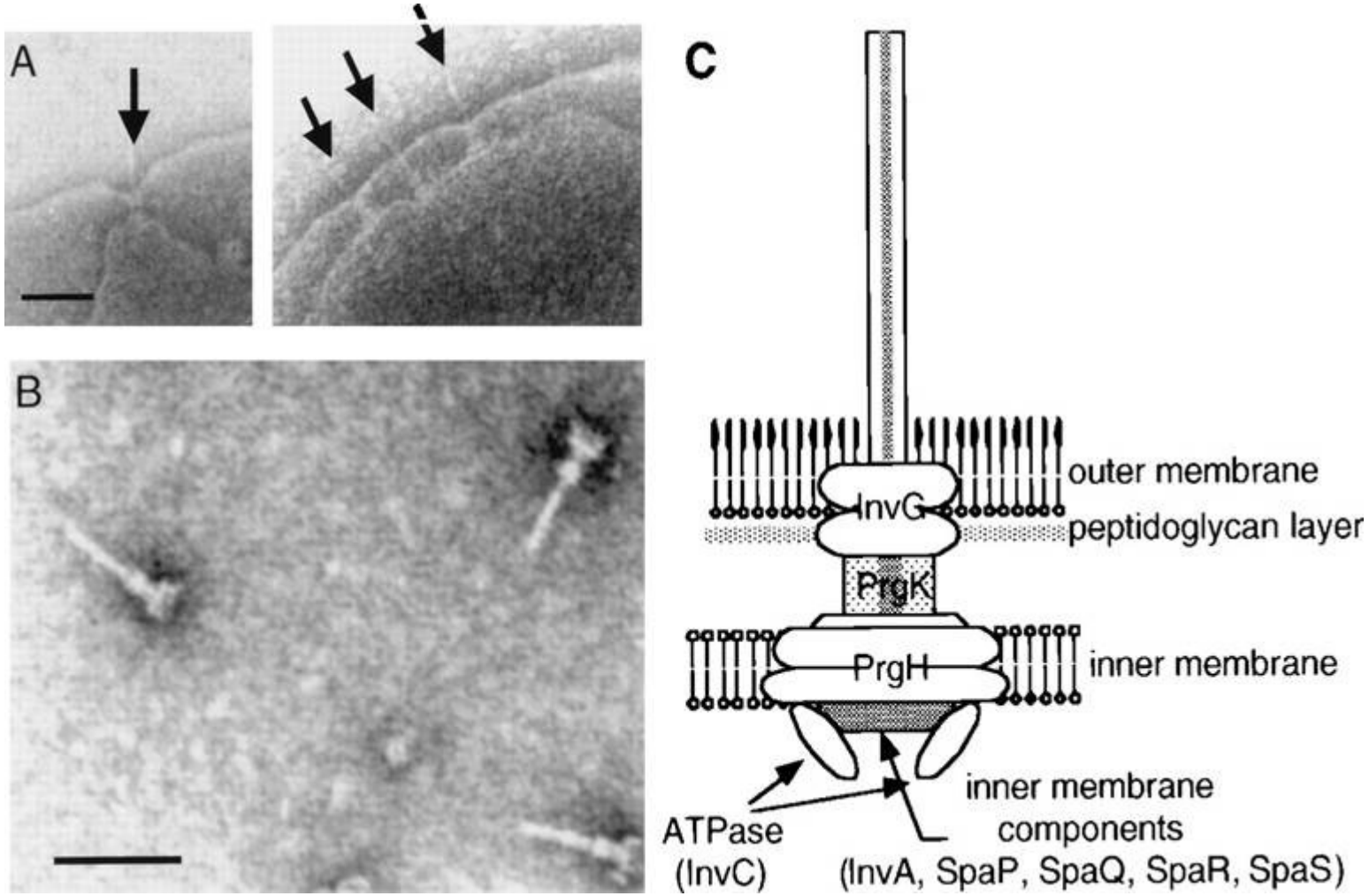
- ✓ Sensibilité & PK/PD
- ✓ EUCAST…..
- ✓ Nouvelles molécules
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

Facteurs extracellulaires de virulence

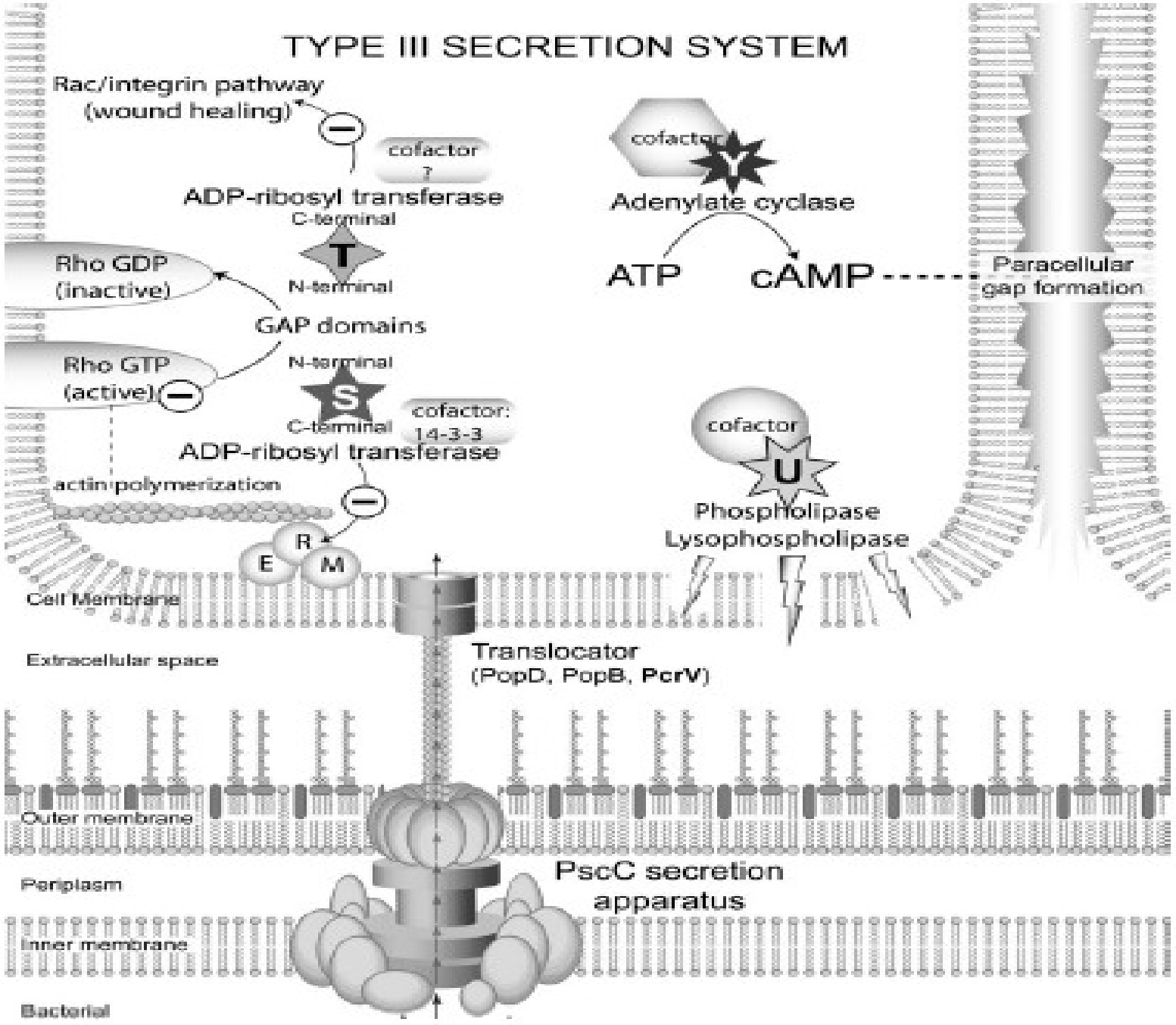


Lazdunski Ann Fr Anesth Réanim 2003,22,5

TTSS: a needle



Kubori *et al.* Science 1998,**280**,602



E. Kipnis et al., Med Mal Infect

Persistent Infection with *Pseudomonas aeruginosa* in Ventilator-associated Pneumonia

Ali A. El Solh[1], Morohunfolu E. Akinnusi[1], Jeanine P. Wiener-Kronish[2], Susan V. Lynch[2], Lilibeth A. Pineda[1], and Kristie Szarpa[1]

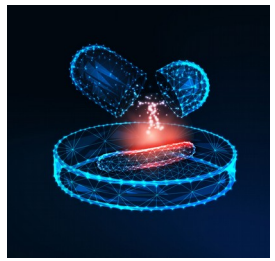
34 patients with VAP

25 TTSS+

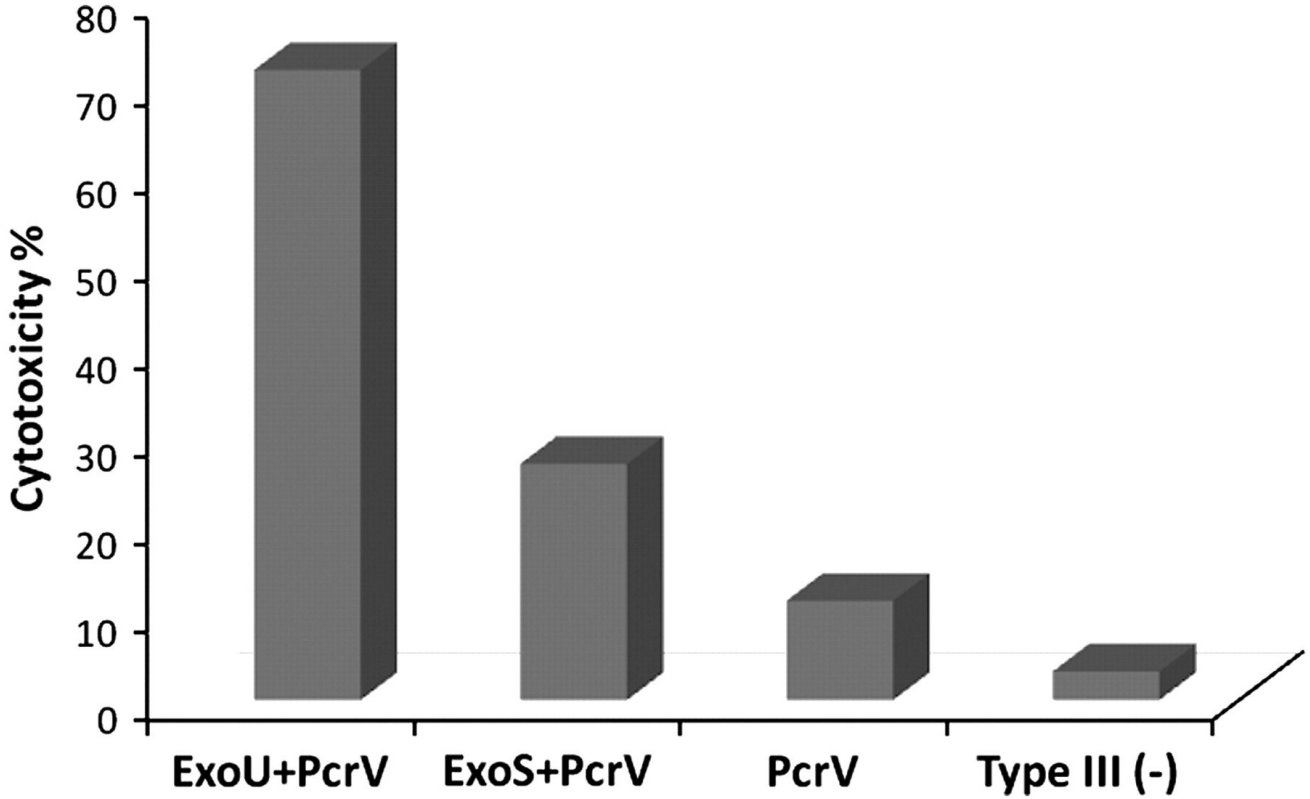
9 TTSS-

Adequate antimicrobial therapy

13/25
+ at day 8

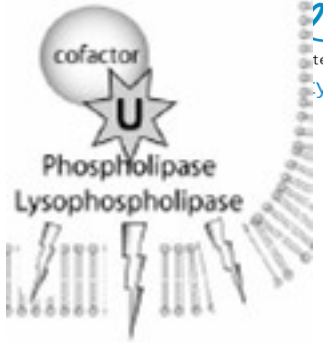


0/9
+ at day 8



Cytotoxicity of Pseudomonas aeruginosa isolates toward human neutrophils. ExoS = exoenzyme S; ExoU = exoenzyme U.

El Sohl et al, Am J Respir Crit Care Med 2008, 178:51



35 patients ventilés
Pneumonie à *P.aeruginosa*

Production de Protéines
Issues du système de sécrétion
de type III

+
27/35

-
8/35

22 Sévère (81%)

5 Modérées (19%)

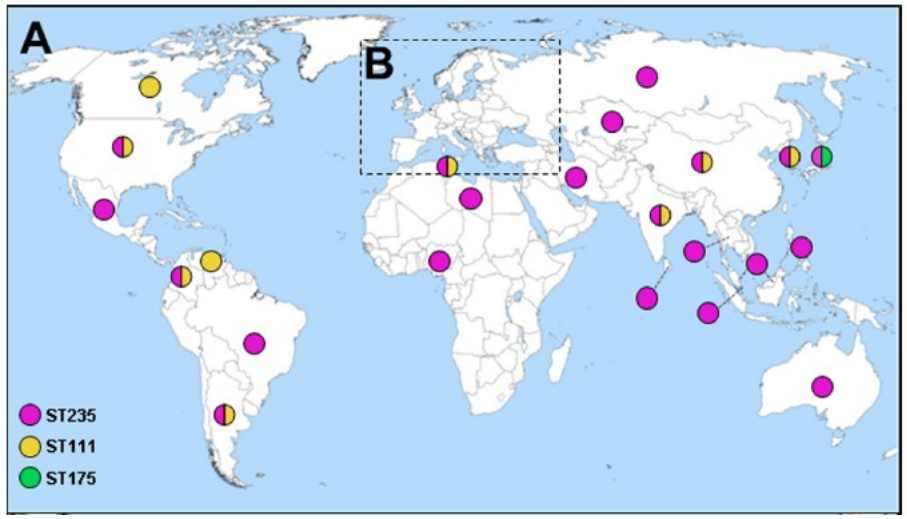
3 Sévères (38%)

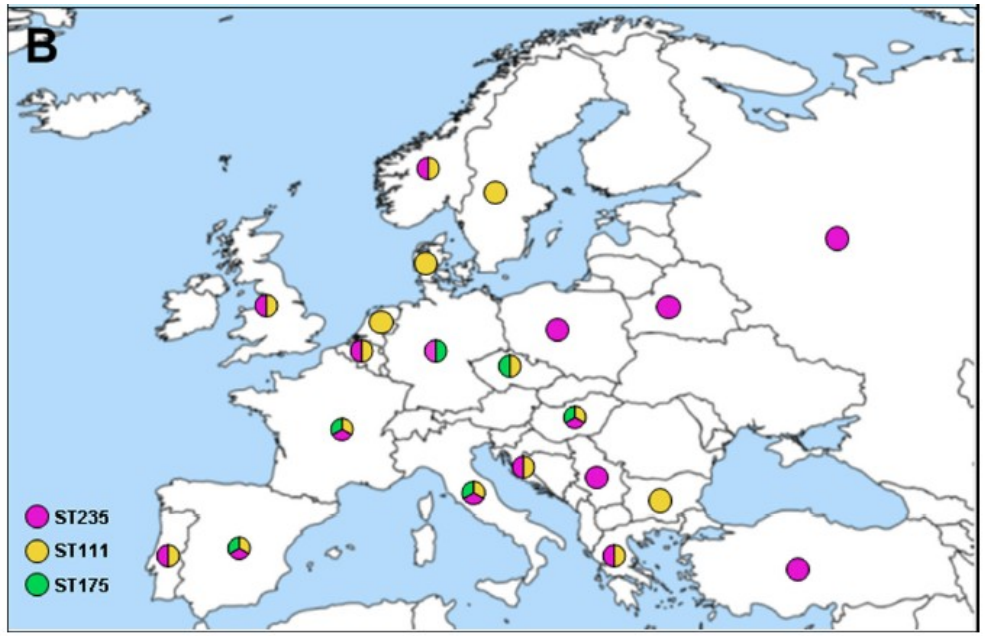
5 Modérées (62%)

ExoU : 10/35 (29%) associée à 90% de formes sévères

Hauser et al, Crit Care Med 20

The increasing threat of *Pseudomonas aeruginosa* high-risk clones





Oliver et al, Drug Resistance Updates 21–22 (2015

Understanding the acute inflammatory response to *Pseudomonas aeruginosa* infection: differences between susceptible and multidrug-resistant strains in a mouse peritonitis model

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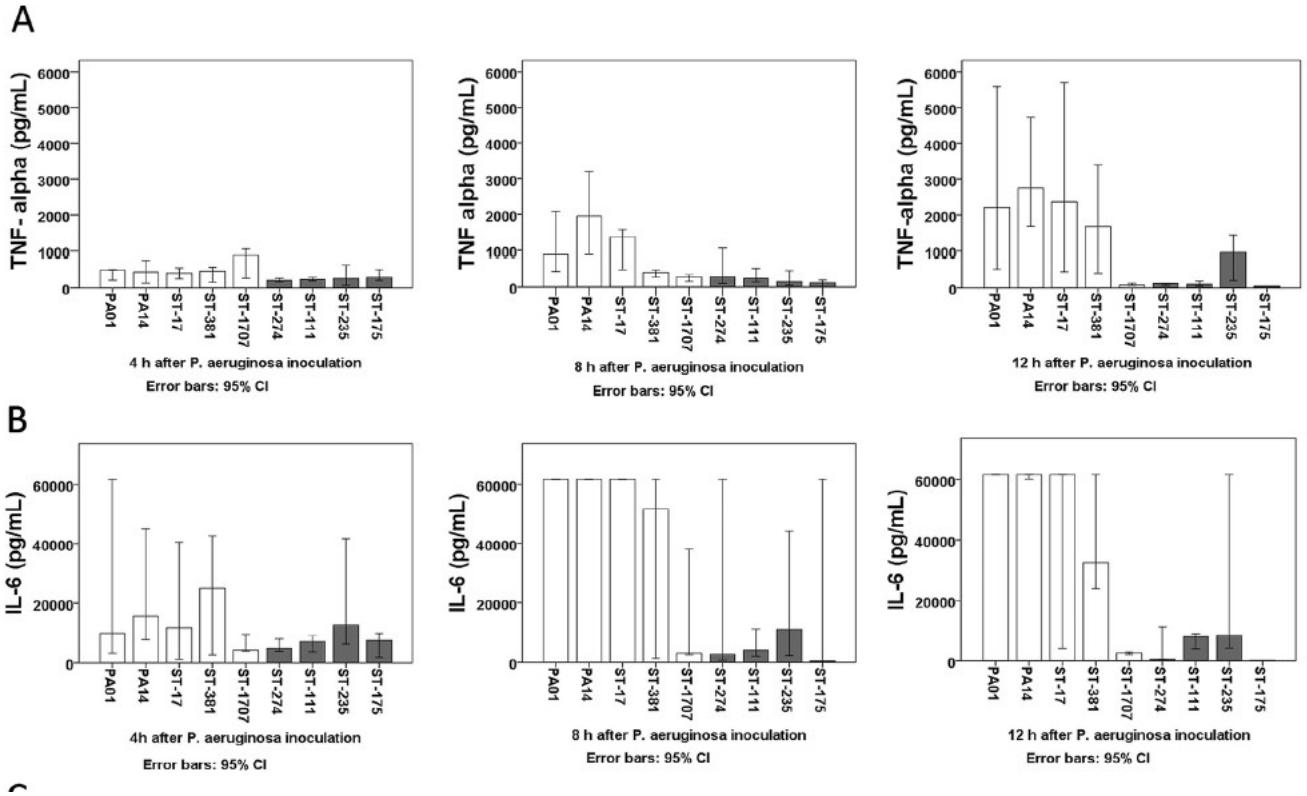
- ✓ Nine *P. aeruginosa* strains
  - o 2 reference strains (PAO1 and PA14)
  - o 7 clinical strains: 3 clinical multisusceptible strains, 1 MDR strain, 3MDR high-risk clones (ST111, ST235 and ST175).
- ✓ Mouse peritonitis model



Gomez-Zorilla et al, International Journal of Antimicrobial Agents

Bacteraemia due to extensively drug-resistant *Pseudomonas aeruginosa* sequence type 235 high-risk clone: Facing the perfect storm

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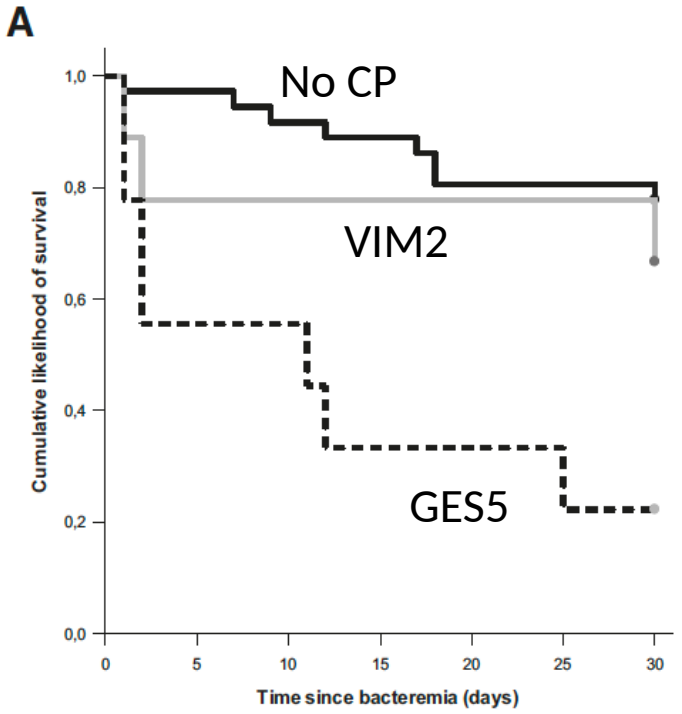
- ✓ Retrospective analysis
- ✓ 64 patients with bacteremia
  - Non-XDR (40)
  - XDR
    - 10 VIM-2 CP (ST175)
    - 11 GES-5 CP (ST235)
    - 3 no CP
- ✓ ST235: 100 ExoU+
- ✓ Susceptibility XDR
  - Cefta-avi 58.3%
  - Cefto-tazo 12.5%
- ✓ 30d mortality
  - XDR: 62.5%
  - Non-XDR: 30%

- ✓ 30d mortality
  - ST175 30%
  - ST235 82%



Recio et al, International Journal of Antimicrobial Agents 52

High risk clones

Colistin plus meropenem combination is synergistic in vitro against extensively drug-resistant *Pseudomonas aeruginosa*, including high-risk clones

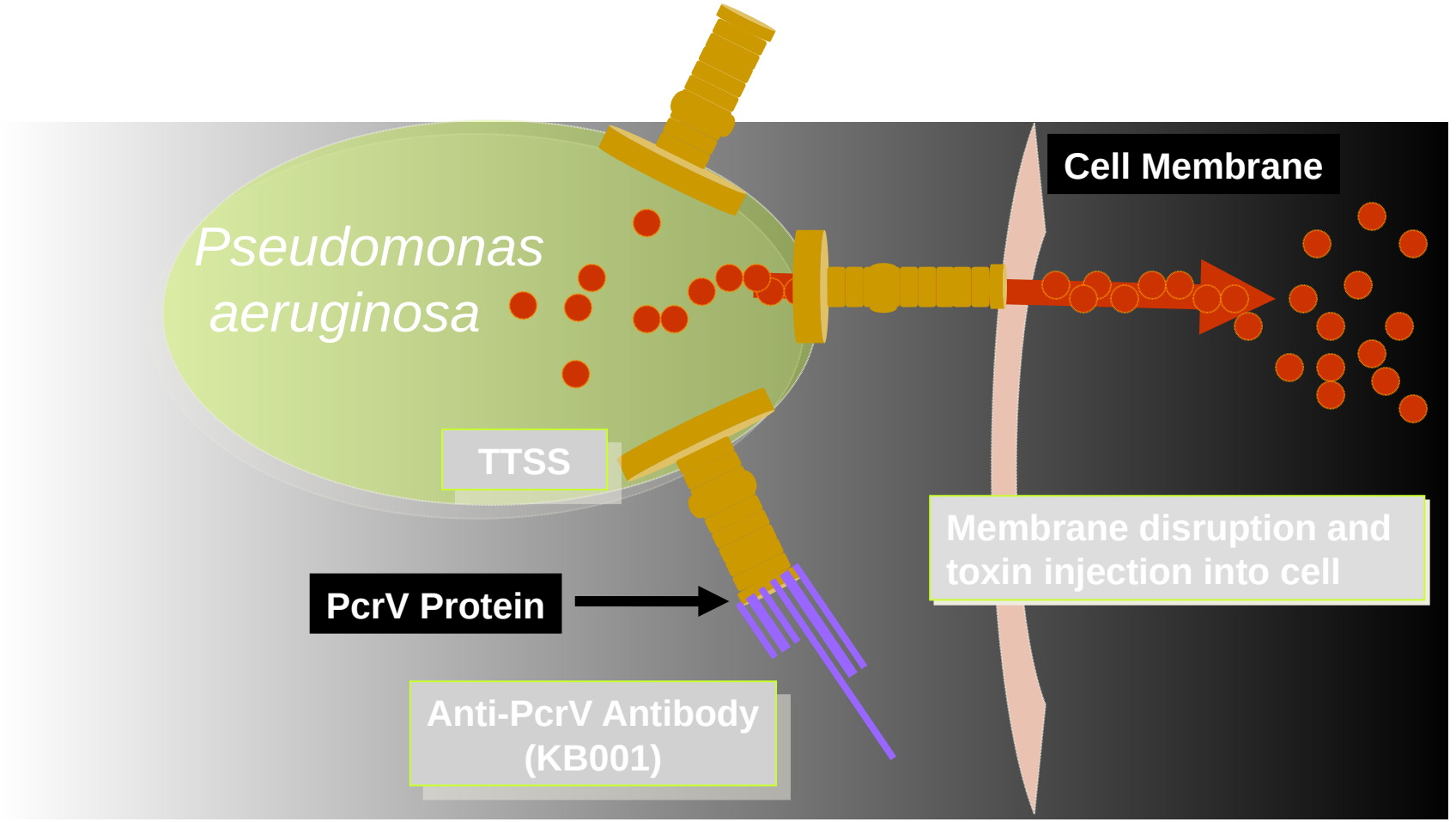
María M. Montero[a,*], Sandra Domene Ochoa[a], Carla López-Causapé[b], Brian VanScoy[c], Sonia Luque[d], Luisa Sorlí[a], Núria Campillo[d], Eduardo Padilla[e], Núria Prim[e], Concepción Segura[e], Virginia Pomar[f], Alba Rivera[f,g], Santiago Grau[d], Paul G. Ambrose[c], Antonio Oliver[b], Juan P. Horcajada[a,*]

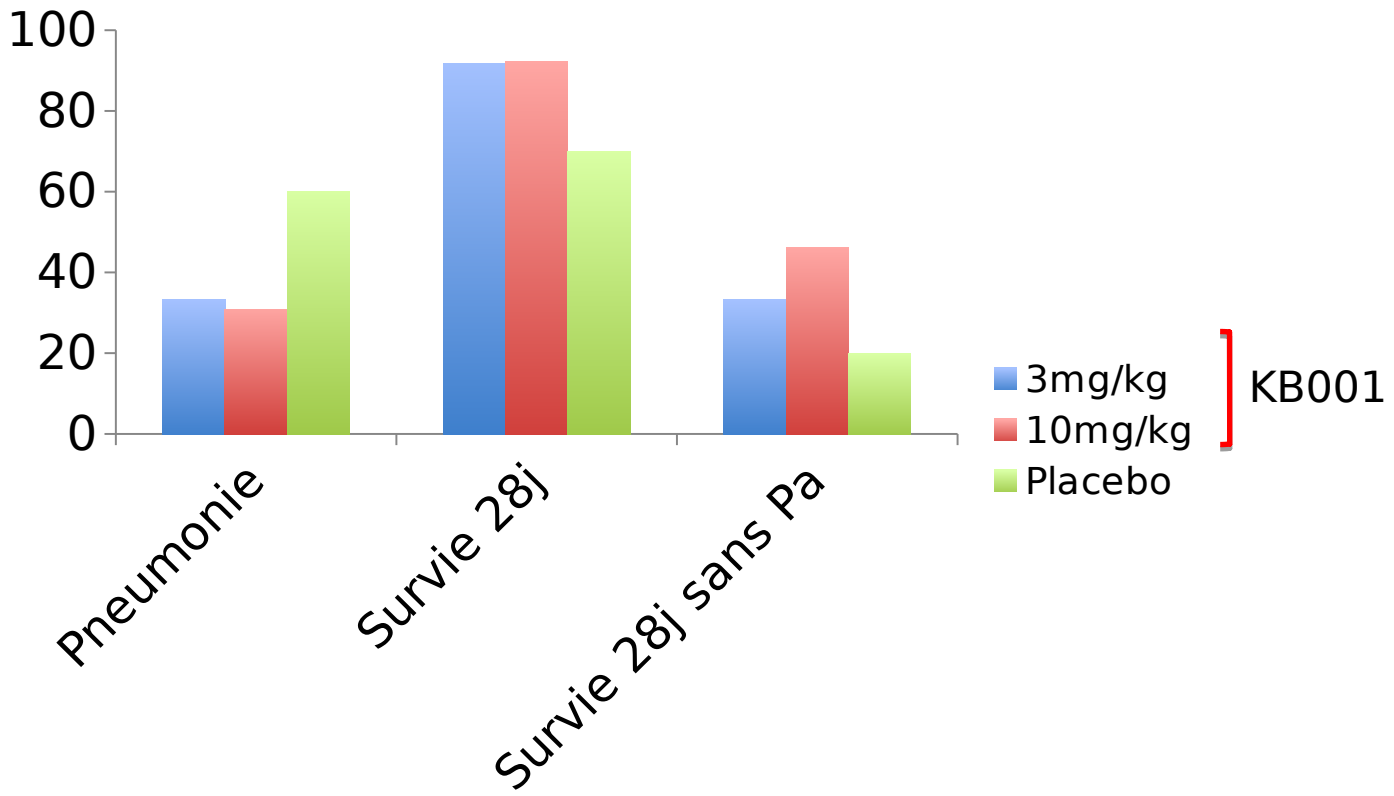
Journal of Global Antimicrobial Resistance 18 (2019) 37–44

Efficacy of Ceftolozane-Tazobactam in Combination with Colistin against Extensively Drug-Resistant *Pseudomonas aeruginosa*, Including High-Risk Clones, in an *In Vitro* Pharmacodynamic Model

María Montero,[a] Sandra Domene Ochoa,[a] Carla López-Causapé,[b] Brian VanScoy,[c] Sonia Luque,[d] Luisa Sorlí,[a] Núria Campillo,[d] Ariadna Angulo-Brunet,[h] Eduardo Padilla,[e] Núria Prim,[e] Virginia Pomar,[f] Alba Rivera,[g] Santiago Grau,[d] Paul G. Ambrose,[c] Antonio Oliver,[b] Juan P. Horcajada[a]

Antimicrobial Agents and Chemotherapy, April 2020 Vol 64 Issue 4 e02542-19


Pseudomonas aeruginosa
Cell Membrane
TTSS
PcrV Protein
Membrane disruption and toxin injection into cell
Anti-PcrV Antibody (KB001)



Crit Care Med 2012 Vol. 40, No. 8

Anti-PcrV Antibody in Cystic Fibrosis: A Novel Approach Targeting *Pseudomonas aeruginosa* Airway Infection

Carlos E. Milla, MD,[1]* James F. Chmiel, MD,[2] Frank J. Accurso, MD,[3] Donald R. VanDevanter, PhD,[2]
Michael W. Konstan, MD,[2] Geoffrey Yarranton, PhD,[4] David E. Geller, MD,[5] and
for the KB001 Study Group†

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- ✓ Two cohorts of 12 subjects were planned: each randomized 2:1 to receive a single intravenous (IV) infusion of KB001 or placebo.
- ✓ Subjects randomized to receive KB001 received 3 mg/kg in the first cohort and 10 mg/kg in the second cohort.

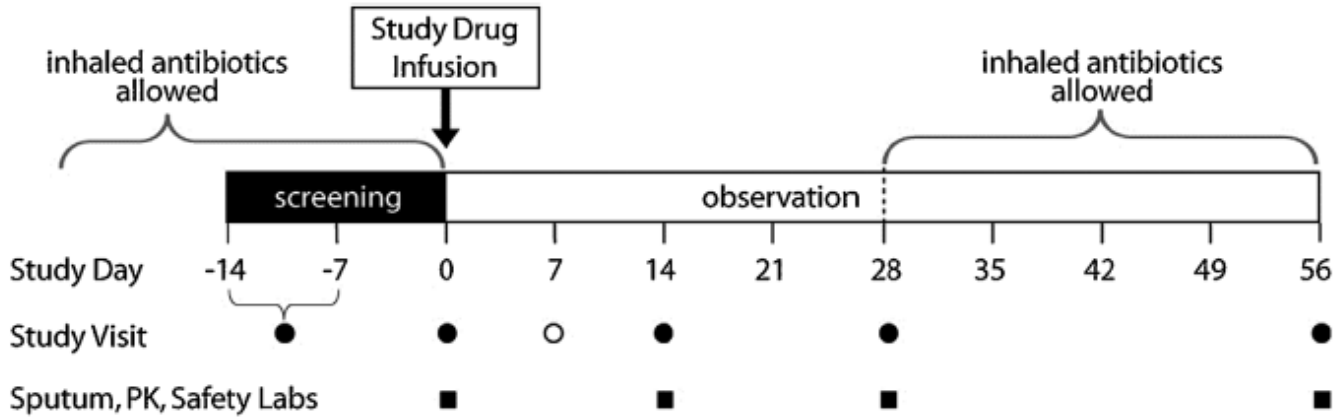


Fig. 1. Schematic of study design. On Day 0 subjects were randomized to receive KB001 or placebo. Filled circles, clinical study visits. Open circle, telephone interview. Filled squares, times of sample collection for safety and efficacy analyses.

Pediatric Pulmonology 49:650–658 (2014)

canton de vaud

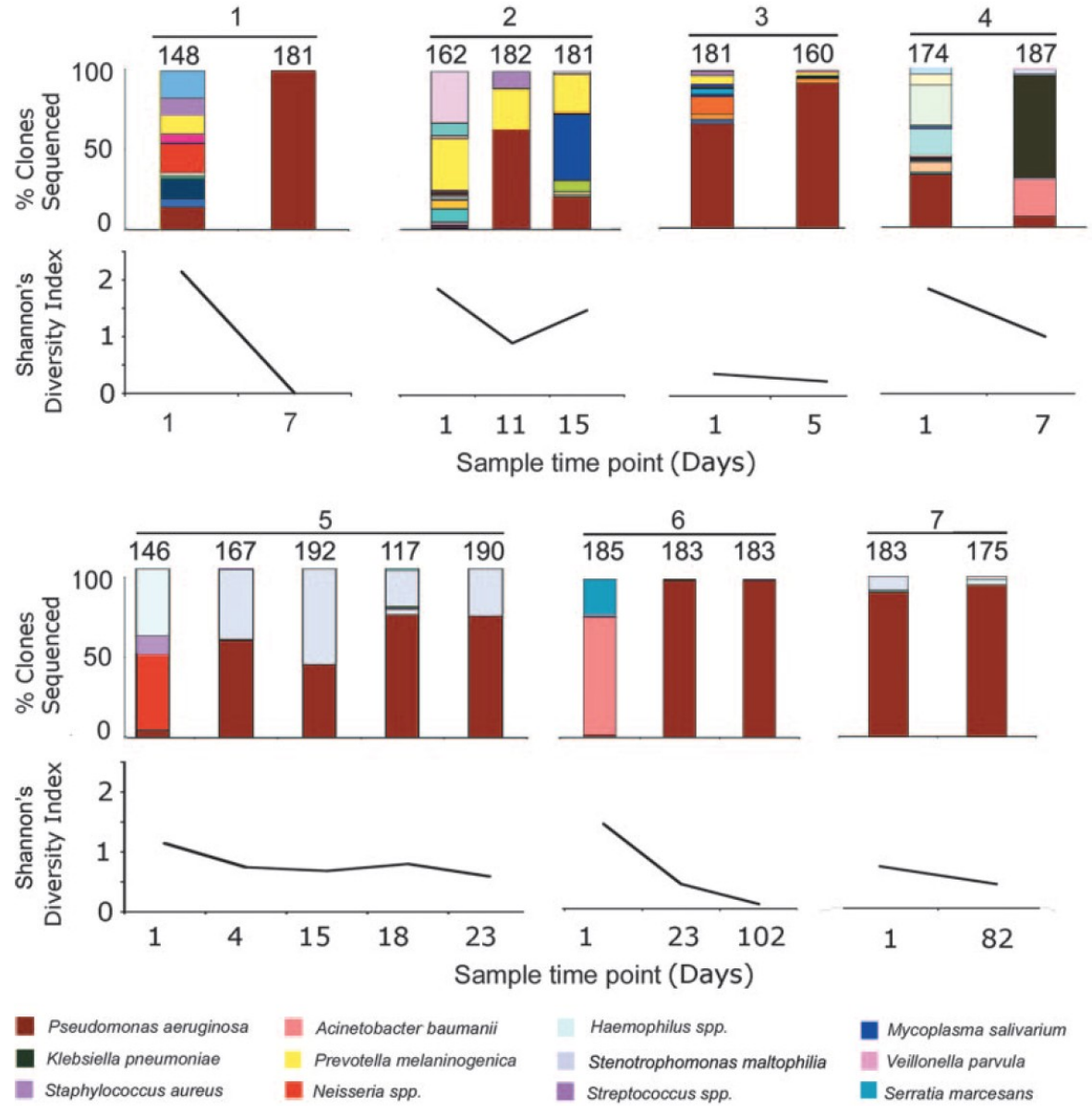
Loss of Bacterial Diversity during Antibiotic Treatment of Intubated Patients Colonized with *Pseudomonas aeruginosa*[▽]

J. L. Flanagan,[1]† E. L. Brodie,[2]† L. Weng,[3] S. V. Lynch,[1] O. Garcia,[1] R. Brown,[1] P. Hugenholtz,[3] T. Z. DeSantis,[2] G. L. Andersen,[2] J. P. Wiener-Kronish,[1] and J. Bristow[3]*

TABLE 1. Patient information and antimicrobial treatment

Patient	No. of days after enrollment (sample no.)	Sex	Patient age	Antimicrobial treatment	
				Within 24 h before study enrollment	Following sampling (sensitivity[a])
1	1 (1)	Female	57 yr	Cefazolin, piperacillin-tazobactam	Piperacillin-tazobactam (S), fluconazole, cefazolin
	7 (2)				Cefazolin (S), fluconazole (S), levofloxacin (S)
2	1 (1)	Male	79 yr	Cefazolin, ceftazidime	Antifungal, ceftazidime (S), vancomycin
	11 (2)				Ceftazidime (R), vancomycin, piperacillin-tazobactam (S), ciprofloxacin (S)
	15 (3)				Vancomycin, piperacillin-tazobactam, ciprofloxacin
3	1 (1)	Female	54 yr	None	Ciprofloxacin (S)
	5 (2)				Ciprofloxacin
4	1 (1)	Male	55 yr	None	Piperacillin-tazobactam, vancomycin
	7 (2)				Piperacillin-tazobactam
5	1 (1)	Female	85 yr	Clindamycin	Clindamycin, piperacillin-tazobactam (S)
	4 (2)				Piperacillin-tazobactam (S), vancomycin, ciprofloxacin (S)
	15 (3)				None
	18 (4)				None
	23 (5)				None
6	1 (1)	Female	45 yr	None	Meropenem (I), fluconazole, linezolid
	23 (2)				Tobramycin(S), imipenem (I), cefpirome, cefazolin, cefepime (I)
	102 (3)				Timentin, trimethoprim-sulfamethoxazole, imipenem, vancomycin, fluconazole, cefepime, cefpirome, amphotericin B, tobramycin
7	1 (1)	Female	2 mo	Ampicillin, gentamicin, trimethoprim-sulfamethoxazole	Ampicillin (R), gentamicin
	82 (2)				Gentamicin (S)

[a] S, sensitive; R, resistant; I, indeterminate.



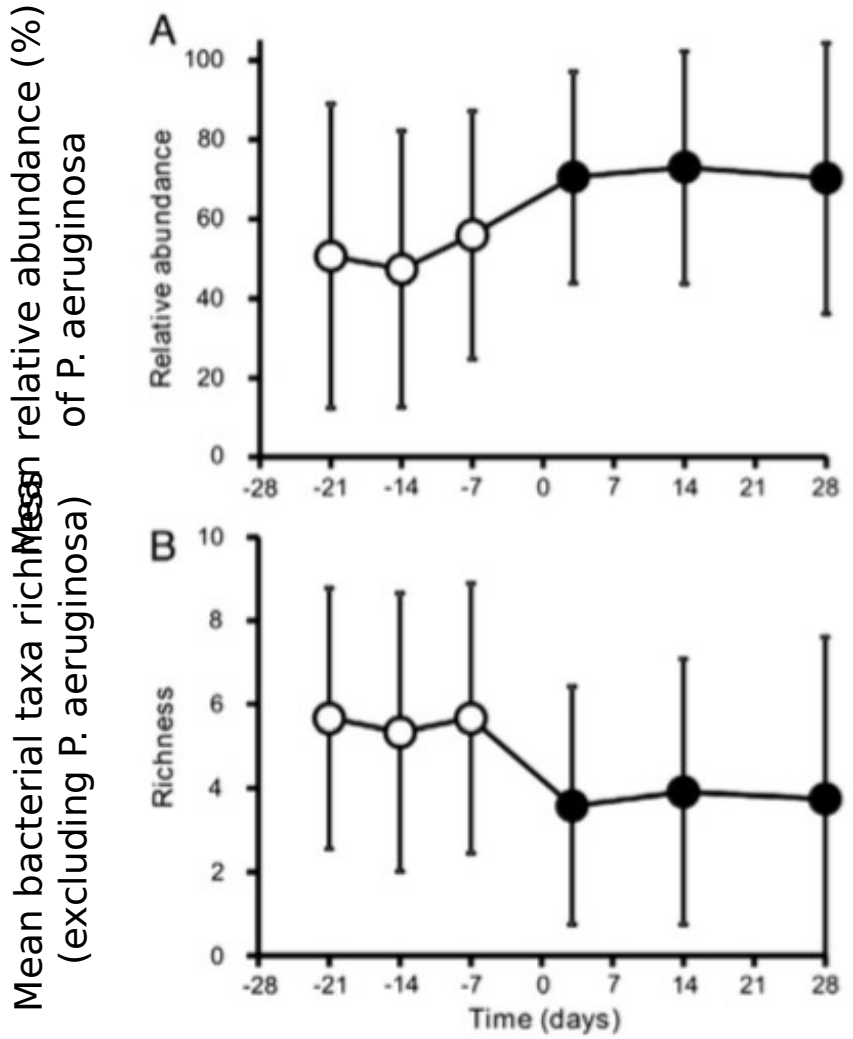
- ✓ We hypothesize that reduced microbial diversity under antibiotic selection in the airways may contribute directly to pathogen selection through the loss of microbial competition.

JOURNAL OF CLINICAL MICROBIOLOGY, June 2007, p. 1954–1962

Impact of antibiotic treatment for pulmonary exacerbations on bacterial diversity in cystic fibrosis

T.W.V. Daniels [a], G.B. Rogers [b,*], F.A. Stressmann [c], C.J. van der Gast [d], K.D. Bruce [b], G.R. Jones [e], G.J. Connett [a], J.P. Legg [a], M.P. Carroll [a]

- ✓ Relative abundance of viable P. aeruginosa and non-pseudomonal species in sputa from 12 adult CF subjects
- ✓ Time points:
  - 21, 14, and 7 days prior to antibiotics
  - day 3 of treatment, the final day of treatment
  - 10–14 days afterward



Journal of Cystic Fibrosis 12 (2013) 22–28

canton de vaud

Respiratory microbiota resistance and resilience to pulmonary exacerbation and subsequent antimicrobial intervention

Leah Cuthbertson[1,2], Geraint B Rogers[3], Alan W Walker[4,5], Anna Oliver[1], Laura E Green[6], Thomas WV Daniels[7], Mary P Carroll[7], Julian Parkhill[4], Kenneth D Bruce[2] and Christopher J van der Gast[1]

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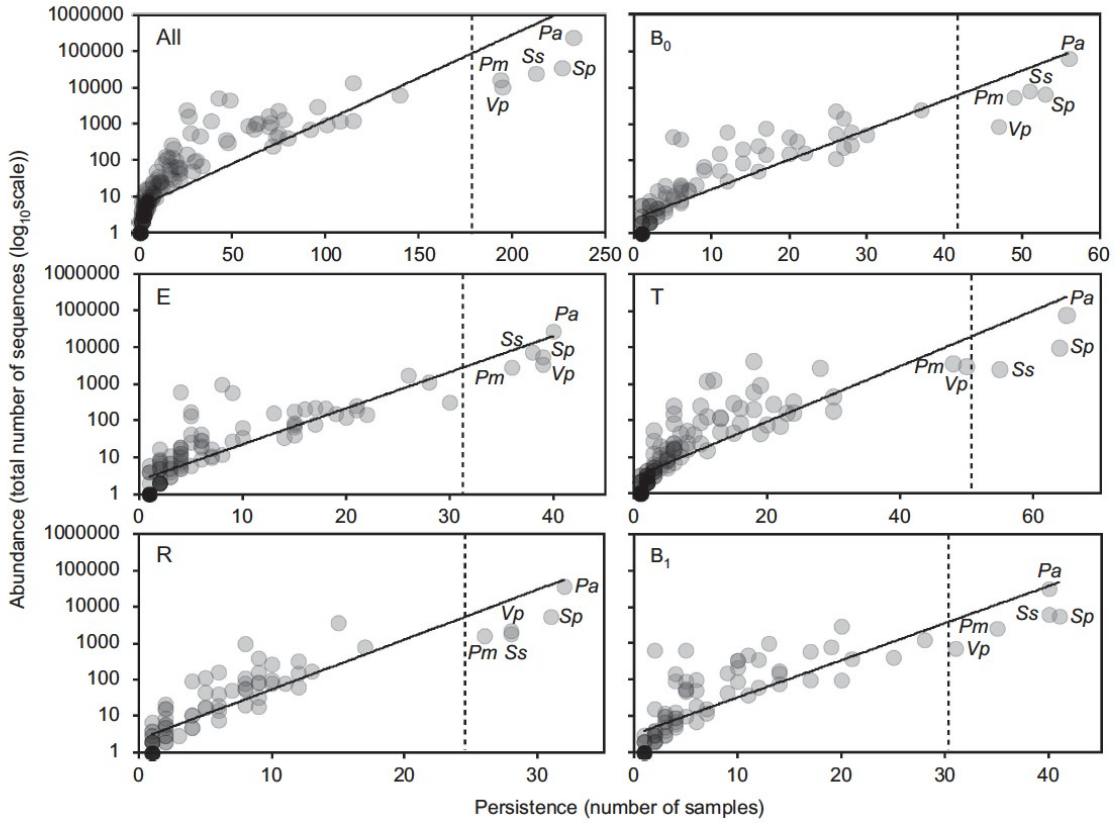
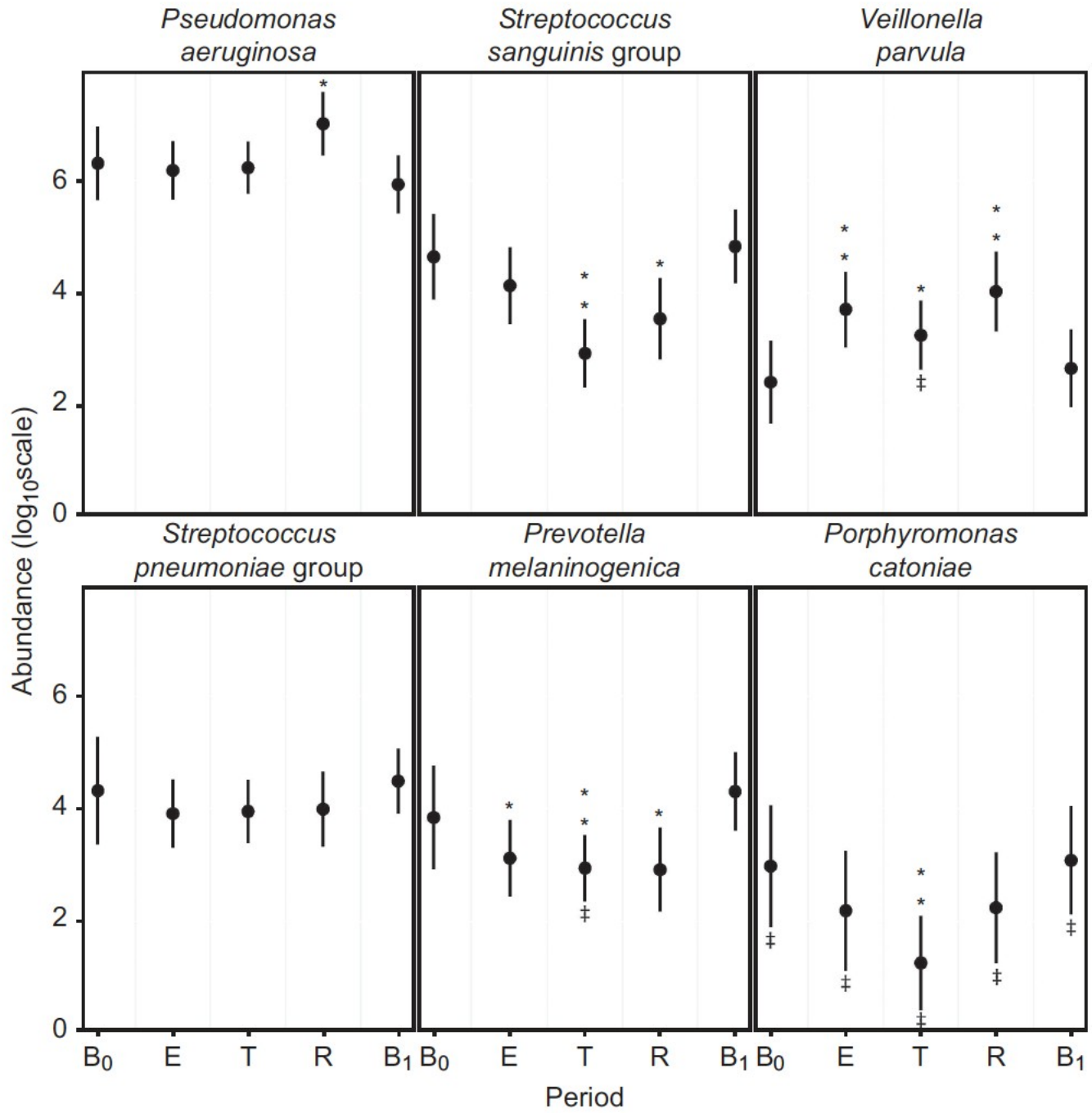
- ✓ (B0) baseline pre-CFPE (n = 56)
- ✓ (E) CFPE, 30 days prior to treatment (n = 41)
- ✓ (T) CFPE treatment period (n = 67)
- ✓ (R) recovery, 30 days post-CFPE treatment (n = 32)
- ✓ (B1) baseline post-CFPE (n = 41)



The ISME Journal (2016) 10, 1081–1091



ISME Journal (2016) 10, 1081–1091

Conclusion

- ✓ Sensibilité & PK/PD:
  - Nombreuses résistances naturelles
- ✓ EUCAST:
  - Faire circuler l'information
- ✓ Nouvelles molécules:
  - Problème persistant des MBL
- ✓ Durée:
  - Courte?
- ✓ Associations:
  - Plutôt non
- ✓ Thérapeutiques alternatives:
  - Recherche